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Preface

The University of Texas Medical School at Houston (UTMSH) Summer Research Program provides intensive, hands-on laboratory research training for MS-1 medical students and undergraduate college students under the direct supervision of experienced faculty researchers and educators. These faculty members’ enthusiasm for scientific discovery and commitment to teaching is vital for a successful training program. It is these dedicated scientists who organize the research projects to be conducted by the students.

The trainee’s role in the laboratory is to participate to the fullest extent of her/his ability in the research project being performed. This involves carrying out the technical aspects of experimental analysis, interpreting data and summarizing results. The results are presented as an abstract and are written in the trainees’ own words that convey an impressive degree of understanding of the complex projects in which they were involved.

To date, more than 1,900 medical, college, and international medical students have gained research experience through the UTMSH Summer Research Program. Past trainees have advanced to pursue research careers in the biomedical sciences, as well as gain an appreciation of the relationship between basic and clinical research and clinical practice.

UTMSH student research training is supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and/or by financial support from the Dean and the departments and faculty of the medical school and School of Dentistry.

Biomedical science education remains a vital and integral part of our nation’s interests. The UTMSH Summer Research Program, and the dedication of our faculty and administration exemplify the institution’s commitment to training and educating the future leaders in our biomedical scientific communities.

Gary C. Rosenfeld, Ph.D.
Director, Summer Research Program
Associate Dean for Educational Programs
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Acknowledgements

This publication marks the completion of the twenty-sixth year of The University of Texas Medical School at Houston’s (UTMSH) Summer Research Program. The longevity and success of the program are rooted in the overwhelming support received from the deans, faculty, staff and students of the medical school.

Indicative of this support is the administrative assistance and financial support for the Program’s college and medical students provided by UTMSH. Sincere appreciation is expressed to Dean Barbara J. Stoll M.D. and Patricia M. Butler, M.D., Vice Dean, Office of Educational Programs who continue to ensure the yearly success of the Summer Research Program.

Major financial assistance for medical students has also been provided through a short term research grant by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK; 5 T32 DK007676).

Negotiated cooperative agreements with several international medical schools have been set up to offer tailored research programs at UTMSH for selected foreign medical students who interact fully with the other students in the Summer Research Program.

The success of the Summer Research Program depends primarily on the faculty who volunteer to mentor the trainees. These dedicated educators organize and guide the research projects that includes for each student data analysis, preparation of an abstract and public presentation of results. Our sincere appreciation to all faculty mentors.
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Lab Research Ownership

Publication and/or Disclosure

Each student participating in this program is required to read, agree to, and sign this disclosure form. The original signed copy is on file in the Summer Research Program office; the student and their faculty mentors are each furnished with a copy.

“In reference to the laboratory research you will perform this coming summer through The University of Texas Medical School at Houston’s Summer Research Program, you are required to comply with the standard restrictions regarding participation in the Summer Research Program:

“All of your laboratory research is CONFIDENTIAL and although your abstract will be available through our website, you cannot independently disclose or publish any research findings or data in any form (including at meetings or conferences) without the express prior written approval of The University of Texas Medical School at Houston. If you wish to submit your abstract to any third party, you must first contact your faculty mentor no less than three (3) weeks prior to any deadlines in order to obtain the necessary written approvals.

“Because your research was generated from ideas and funds that originated with your faculty mentor and The University of Texas Medical School at Houston, ownership of any data generated by you during the Summer Research Program belongs to The University of Texas Medical School at Houston or the Principle Investigator (PI).”
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# Medical Students

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Medical Students
ABSTRACT

Imaging CSF Outflow to the Lymphatic System in Swine Using Intrathecal Injection of Indocyanine Green

ALEXANDER BAREIS
McGovern Medical School at UTHealth

Sponsored by: Sun Kuk Kwon, PhD, Eva Sevick-Muraca, PhD, Center for Molecular Imaging – Institute of Molecular Medicine

Supported by: NASA, Translational Research Institute; Quantification of the lymphatic pump strength and its connection to the CSF

Key Words: Lymphatic system, cerebrospinal fluid, indocyanine green, near-infrared fluorescence imaging, swine

Background: Recent research has shown that the cerebrospinal fluid (CSF) and the peripheral lymphatic system are interconnected. Currently, the only modality for visualizing the connection between CSF and the lymphatic system is to perform injections into the cisterna magna, which is invasive to humans. Intrathecal injections are made into the subarachnoid space in the spinal canal and offer non-invasive access to the CSF. To our knowledge, intrathecal injection of indocyanine green (ICG) for imaging CSF outflow into the lymphatics has never been performed.

Objectives: We seek to assess if intrathecal injection of ICG can be used to follow CSF outflow from the CNS into the cervical lymph nodes in the large animal model of swine.

Methods: We conducted non-surgical intrathecal injection of ICG in swine using aseptic techniques. CSF was removed in equal volume to that of the ICG injected to maintain equilibrium regarding intracranial pressure. Near-infrared fluorescence imaging was performed to assess drainage of CSF from the CNS into the lymphatic system in vivo. Imaging occurred at injection lasting up to one hour post-injection. Lymph nodes, CSF, and components of the CNS were later excised and assessed for fluorescence.

Results: We were unable to non-invasively detect CSF drainage to the cisterna magna or to the cervical lymph nodes in vivo due to depth beneath fat tissues, musculature, and spinous processes. However, we detected fluorescence around the coccygeal region in which less fat tissue was present. Excised lymph nodes and harvested CSF displayed marked fluorescence.

Conclusion: CSF and lymph node fluorescence in our animal model suggest CSF outflow from the CNS into the lymphatic system, which was accomplished through non-invasive intrathecal ICG injection.
ABSTRACT
The Effects of Hurricanes on Preeclampsia and Fetal Loss

LISA BIRD
McGovern Medical School at UTHealth
Class of 2020

Sponsored by: James R. Langabeer, PhD, EdD, ACHE, MBA, Dept of Emergency Medicine
Supported by: Dr. Langabeer, Dept of Emergency Medicine
Key Words: Preeclampsia, hurricanes, disaster

The effects of man-made disasters such as nuclear radiation exposure on pregnancy has been studied extensively, but there is little objective information on the effects of natural disasters on pregnancy. Hurricanes frequently occur in the Atlantic Ocean during the period of June – November, posing a risk to large portions of the population. The majority of clinically relevant research has been performed only on hurricanes of historical significance, such as Hurricane Katrina, without inclusion of smaller, more typical hurricanes that patients are more likely to experience in the dataset. We sought to remedy this gap of knowledge, with a focus on preeclampsia and fetal loss outcomes. Preeclampsia remains a leading cause of maternal death in the United States, as well as a risk factor for stillbirth, but there is no test specific or sensitive enough to predict which patients will develop preeclampsia, so physicians rely solely on consideration of risk factors. We are performing multinomial logistic regression as secondary analysis on cohort data from the National Vital Statistics System collected by the U.S. Centers for Disease Control and Prevention to examine preeclampsia incidence and fetal loss outcomes in counties affected by tropical hurricanes, with comparison of outcomes of similar months in examined counties during non-hurricane years. We selected vital statistics data from all U.S. states during years 1995 – 2005. Our models will use multivariate statistical analysis to test the effect of tropical hurricanes on preeclampsia and decipher whether intervening maternal, pregnancy specific, period, or socioeconomic factors contribute to the effect of tropical events on pregnancy outcomes.
ABSTRACT

Analysis of Pediatric Gunshot Wounds in Houston, Texas: A Social Perspective

JOE W. BREWER JR.  McGovern Medical School at UTHealth  Class of 2020

Sponsored by:  David I. Sandberg, M.D., Vivian L. Smith Department of Neurosurgery
Supported by:  David I. Sandberg, M.D., Vivian L. Smith Department of Neurosurgery
Key Words:  Social Analyses of Pediatric GSW in Houston, Tx

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Michelle Sandberg, MD
Marcia L. Kerr, RN
David I. Sandberg, MD

Introduction: Gunshot wounds (GSW) are a leading cause of injury and death in children. This study explored social factors contributing to these tragic events.

Methods: We reviewed medical records of GSW victims between ages 0 to 15 who presented to a Level 1 pediatric trauma center between 1999 and 2016. Social work and case manager notes were reviewed to obtain data about factors contributing to the event.

Results: 358 children with GSW were treated between 1999 and 2016. Patients ranged from 2.5 months to 15 years old (mean=10.8 years). 292 patients (81.6%) were male, and 66 (18.4%) were female. The most common anatomic location of injury was the head and/or neck (n=166;46.4%). 7.8% (n=28) died, 31.6% (n=113) survived with a new disability, and 58.1% (n=208) survived without disability. Disability outcome was unknown in 9 patients (2.5%). 38.3% of injuries (n=137) were caused by handguns, 25.1% (n=90) by BB guns, and 12.6% (n=45) by shotguns or rifles. The weapon utilized was unknown in 24.0% (n=86). Firearms were secured in locked gun safes in just 1.7% of cases (n=6). 39.9% (n= 143) were unsecured, and this information was not available in 58.4% (n=209). 45.5% of incidents (n=163) were intentional; 17 of these (4.7%) were suicide attempts. 48.9% of incidents (n=175) were accidental, and intent was unknown in 5.6% (n=20). The majority (n=226) of incidents (63.1%) occurred in a family residence. An adult was supervising the victim in only 26.3% of cases (N=94). Criminal charges were filed in 36 cases (10.1%). 15 victims (4.2%) were placed in CPS custody. Only 12.0% of charts (N=43) mentioned gun safety education being provided to the family.

Conclusion: Many pediatric GSW can be prevented with more attention paid to securing firearms, increased community education efforts, and other safety measures.
ABSTRACT
Long-term Impact of Pancreatectomy for Benign Cystic Lesions.

ASHLEY BROWN
McGovern Medical School at UTHealth
Class of 2020

Sponsored by: William E. Fisher, Elkins Pancreas Center, Baylor College of Medicine
Supported by: William E. Fisher, Elkins Pancreas Center, Baylor College of Medicine
Key Words: Pancreatectomy, pancreatic cystic lesions, diabetes, surgical outcomes

Background: Cross-sectional imaging technology has improved pancreatic cyst identification. Due to the fear that these cysts may develop into cancerous lesions, many are referred for pancreatectomy. Understanding the long-term outcomes of pancreatectomy is important to consider when removing a benign lesion. Previous studies have been limited by a 5-year follow-up period. This study aimed to quantify the effects of nutritional status, quality of life (QOL), and gland function after pancreatectomy for benign cysts.

Methods: Patients ≥ 3 years post-pancreatectomy for benign cystic neoplasms were selected from a prospectively maintained database at a high-traffic pancreas center. Pancreatic endocrine and exocrine function were evaluated. A history of chronic pancreatitis or PNET were exclusionary. Participation was obtained through telephone contact. Nutritional status, as well as pre- and post-operative QOL, was assessed using a modified Subjective Global Assessment (SGA) and the Functional Assessment of Cancer Therapy (FACT-Hep) questionnaires.

Results: Of 99 eligible patients, 46 (47%) enrolled. Median follow-up was 7 (2-12) years. At follow-up, 23 (50%) patients were deemed well-nourished (SGA A) while 33 (48%) suffered from mild-moderate malnourishment (SGA B). 29 (63%) of patients completed pre- and postoperative QOL surveys. Post-pancreatectomy QOL scores increased by a mean of 40 points (95% CI 31 to 50, p<0.005). 6 (13%) of patients underwent pancreatic enzyme replacement. New-onset diabetes was present in 14 (35%) of patients. Median diagnosis time was 11 (1-24) months post-resection.

Conclusion: While pancreatectomy for benign cystic disease may improve QOL, malnutrition and pancreatic insufficiency are present in a large proportion of the population when prospectively followed for greater than 5 years.
Regulation of dendritic arborization of hippocampal neurons by TRPC4 channels

NICOLAS CASSATA  
McGovern Medical School at UTHealth  
Class of 2020

Sponsored by: Michael Zhu; Department of Integrative Biology & Pharmacology  
Supported by: Michael Zhu  
Key Words: TRPC4, dendritic arborization, mGluRs, growth cones

The notion that dendritic growth is regulated by extracellular cues that allow targeted growth for synaptogenesis is well supported, but the underlying mechanisms and molecular details of the pathways involved to bring about the final outcome remain unclear. It is clear, however, that dendritic growth is highly dynamic, including not only extension but also retraction and branching as the dendrites look to form synapses with other neurons. The dendritic arbor is the term given to the morphologically dynamic collection of all of the dendrites of a neuron. Dendrites, like axons, often mediate both anterograde and retrograde membrane flow with the formation of distal membrane structures called growth cones that may affect the subsequent growth or retraction. As the major excitatory neurotransmitter, glutamate also exerts a role in the overall morphology of the dendritic arbor, and until recently this has only been investigated with regard to ionotropic glutamate receptors, such as NMDA and AMPA receptors. However, metabotropic glutamate receptors (mGluRs) are also widely expressed in neuronal dendrites and they likely play roles in dendritic arborization too. As one of the major Ca2+-permeable channels activated downstream from mGluR stimulation that signals through both Gq/11 and Gi/o proteins, transient receptor potential canonical (TRPC4) represents an excellent candidate for mediating the effect of mGluR activation. Indeed, either genetic ablation or overexpression of TRPC4 caused a decrease in neurotrophin-induced dendritic arborization of cultured hippocampal neurons. Here, we compared dendritic morphology and growth patterns in primary hippocampal neuron cultures prepared from wild type (WT) and TRPC4 knockout (TRPC4KO) mice. To allow time-lapse fluorescence imaging of dendritic growth in individual neurons, we transfected the neurons with membrane associated green fluorescent protein (GFP). The neurons were grown in an environmental chamber with controlled conditions (37°C, and 5% CO2) while time lapse fluorescence video images were taken with a confocal microscope. Growth cone sizes and branch lengths were analyzed frame by frame using Image J. Either in the absence or presence of 5 µM glutamate in the culture medium, the proportion of dendrites showing growth cones and the growth cone sizes did not differ significantly between WT and TRPC4KO neurons. However, the short-lived growth cones are more common in TRPC4KO than in WT neurons. Moreover, when compared to WT, TRPC4KO dendrites exhibited an overall decrease in growth rate in response to glutamate. In addition, while the WT dendrite grew continuously over a period of 6 hrs, TRPC4KO dendrites tended to halt after the initial growth period of about 2 hrs. Surprisingly, the application of NMDA receptor blocker, AP5, extended the growth of TRPC4KO dendrites beyond the 2 hr period but arrested the growth of WT dendrites at around 2 hrs. These results suggest that TRPC4 channels and NMDA...
receptors play distinct, yet interrelated, roles in dendritic arborization of hippocampal neurons responding to the common stimulus, glutamate. Their combined activities allow precise control of pairing between dendrites and incoming axons, setting the stage for synaptogenesis.
ABSTRACT

Cold and Exercise Exposure Stimulates Lipolysis through Upregulation of Adipose-Derived VEGF-A via Activation of Sympathetic Nervous System (SNS)

Catherine Chang
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Miranda Dam
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Sponsored by: Kai Sun MD, PhD, Center for Metabolic and Degenerative Diseases, Institute of Molecular Medicine

Supported by: NIH (R01DK109001), American Diabetes Association (1-17-JDF-068), Pilot Award from Center of Clinical and Translational Studies at University of Texas Health Science Center at Houston (CTSA UL1 TR000371)

Key Words: Obesity, Angiogenesis, VEGF-A, Lipolysis, Browning

Obesity is a major risk factor for many epidemic diseases including type 2 diabetes and cardiovascular disease (CVD). During obesity development, vascularization by angiogenesis in adipose tissue cannot keep the pace with the rapid speed of fat mass expansion. This may further cause local hypoxia, fibrosis, macrophage accumulation and inflammation which ultimately lead to systemic insulin resistance, the hallmark of type 2 diabetes. Importantly, we recently found that overexpression of a key angiogenetic factor VEGF-A in transgenic mice dramatically improves the vascularization in the obese adipose tissue, which hence protects transgenic mice not only against high-fat diet (HFD)-induced obesity but also insulin resistance. To observe potential inducible effects on VEGF-A, we placed mice under cold and exercise conditions, known methods associated with weight loss. We observed a more multilocular appearance of white adipocytes and significant upregulation of UCP-1, confirming a browning effect on the subcutaneous white adipose tissue (sWAT). These browning effects include increased energy expenditure and metabolic improvement in dissipating excess energy as heat. Furthermore, we found a massive upregulation of VEGF-A stimulating angiogenesis. To potentially mimic the cold and exercise exposure conditions, we used a doxycycline (Dox) inducible adipose tissue specific VEGF-A overexpression mouse model. In these transgenic mice we found that local overexpression of VEGF-A stimulates lipolysis in adipose tissue by upregulating hormone sensitive lipase (HSL) expression and enhancing its phosphorylation levels in adipocytes. As the result, the VEGF-A transgenic mice exhibited smaller adipocytes and reduced total fat mass shortly after VEGF-A induction. Intriguingly, the local norepinephrine (NE) levels in adipose tissue were dramatically increased in the transgenic mice. Immunofluorescent staining (IF) with anti-tyrosine hydroxylase (TH) antibody further showed higher density of neurons innervated in the adipose tissue of the transgenic mice. These findings clearly demonstrate that the sympathetic tone activated by VEGF-A plays a key role in adipose tissue lipolysis, which eventually leads to enhanced energy expenditure. These studies show that cold and exercise conditions stimulating the upregulation of VEGF-A may be potential targets for treating obesity.
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ABSTRACT
A High-Kras Model of Ductal-Derived Pancreatic Adenocarcinoma and Cholangiocarcinoma

Qingzheng Chen  
McGovern Medical School at UTHealth  
Class of 2020

Sponsored by:  Jennifer Bailey, PhD, Department of Internal Medicine
Supported by:  National Institute of Diabetes and Digestive and Kidney Diseases Grant, 5 T35 DK 7676-24
Key Words:  Pancreatic ductal adenocarcinoma, G12V Kras mutation, cholangiocarcinoma

Background and Hypothesis: Chronic inflammation associated with progressive pancreatitis increases the risk of pancreatic ductal adenocarcinoma (PDAC) by 13-fold. PDAC is an extremely deleterious malignancy and is the fourth leading cause of cancer-related mortality; despite an increase in knowledge regarding the pathogenesis, diagnosis, and management of PDAC, there still exists a substantial gap in understanding of its exact tumor biology and progression from chronic pancreatitis in some cases. Greater than 90% of patients with PDAC express activating mutations in \( Kras \); recent literature have revealed that pancreatic acinar cells show greater neoplastic transformative potential than ductal cells in response to Kras mutations, and a two-hit model of PDAC has been described entailing either an additional tumor suppressor loss (\( TP53, SMAD4, CDKN \)) or chronic inflammation in conjunction with Kras mutations. In addition, a novel role for a high Kras \( G12V \) mutation to produce PDAC from acinar cells was recently studied in a murine model. This led us to hypothesize whether this \( G12V \) Kras mutation would transform ductal cells to PDAC and if so, propose a mechanism and therapeutic treatment.

Methods: Expression of an inducible \( Kras^{G12V} \) allele (\( Kras^{hi} \)) in \( Hnf1b:CreER^{12} \) (ductal cell specific) mice was performed using Tamoxifen to induce recombination after 6-8 weeks of normal growth. Mice were sacrificed at numerous timepoints, including day 5, day 7, and time of death, and their pancreatic and liver tissues were fixed, paraffin-embedded, sliced, and analyzed via immunohistochemistry (IHC). Confirmation of high-Kras activity was performed by western blot, and immunofluorescence (IF) analysis confirmed recombination. Several mice were treated with Bay 11-7085, a known NFkB inhibitor, and analyzed in the same manner at equivalent time points.

Results: \( Kras^{G12V} \) mutations in the ductal cells of these mice resulted in not only rapid development of PDAC but also cholangiocarcinoma, with an average mortality at 10-12 days post-recombination. Histological analysis showed a significant increase in the ratio of abnormal papillary projecting cells to normal ductal epithelium from day 5 to time of death in both the pancreatic ducts and bile ducts. Furthermore, stellate-cell induced desmoplasia was significantly intensified in the pancreas, indicated by IF staining of smooth muscle actin (SMA). This rapid development of cancer likely involved upregulation of NFkB expression, confirmed with IHC in both endpoint pancreatic and liver slices. Treatment with Bay 11-7085 ameliorated not only the rapid development of PDAC and cholangiocarcinoma but also the desmoplastic...
reaction, shown by reduced IF of SMA. Future studies of RNA transcriptome analysis and macrophage populations will reveal further insights into the development of PDAC.
ABSTRACT

The Trends of Clinical Biomarkers in Treatment Related Neuroendocrine Prostate Carcinoma

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Sponsored by:  Robert J. Amato, DO, Department of Internal Medicine, Division of Oncology
Supported by:  Robert J. Amato, DO, Department of Internal Medicine, Division of Oncology; McGovern Medical School at UTHealth-Office of the Dean

Key Words:  Treatment Related Neuroendocrine Prostate Carcinoma, biomarkers

Introduction:  Treatment related neuroendocrine prostate carcinoma is thought to develop due to resistance to androgen deprivation therapy and is associated with a poor prognosis in patients with metastatic prostate cancer. Patients with neuroendocrine prostate carcinoma present with low prostate specific antigen (PSA), bone and visceral metastases, prostate enlargement, and resistance to therapy. Cases of neuroendocrine prostate carcinoma often go under-diagnosed in the clinic due to a dearth of reliable biomarkers. However, increasing Neuron Specific Enolase (NSE) and chromogranin A levels have shown to correlate with androgen resistance, disease progression, and Gleason score. We performed a retrospective study to identify patients who developed neuroendocrine differentiation and followed chart biomarker trends over time.

Methods:  Patients with prostate adenocarcinoma undergoing androgen deprivation therapy with Zytiga and Xtandi who developed metastatic castration resistant prostate cancer were selected for the study. Bone scans, CT scans, and MRI studies that were a part of the clinical assessment were analyzed. Results of blood obtained from 4-12 weeks during treatment procedures were assessed for the following markers: PSA, NSE, Chromogranin A, CEA, Testosterone, DH-T, Prolactin, PTH, Sedimentation Rate, C-reactive Protein, and Alkaline Phosphatase. This study was randomized and double-blinded.

Results:  From the cohort of 58 patients, 9 patients showed low, baseline levels of PSA (< 20 ng/mL) with increasing levels of NSE and chromogranin A after Xtandi or Zytiga treatment. Five of the nine patients (55%) presented with progression of bony metastases from the most recent lab measurement. The mortality rate of the patients with neuroendocrine-type patterning was (44%).

Conclusion:  Several patients in this study presented with slight increases in NSE and significant increases in Chromogranin A with baseline levels of PSA. About 55% demonstrated resistance to androgen deprivation therapy which may signify transition to neuroendocrine cell prostate carcinoma and progression of metastases. Biopsy results, Gleason scores, and an expanded profile of treatment are needed to confirm patients with neuroendocrine prostate carcinoma. These biomarkers remain of interest as clinical markers and are currently being further investigated.
ABSTRACT

The Impact of Enhanced Communication and Empowerment in Patient and Family Centered Care

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Sponsored by: Olakunle Idowu, MD, Department of Anesthesiology at MD Anderson Cancer Center

Supported by: The Society of Critical Care Medicine PCOR ICU Collaborative

Key Words: Improvements to patient and family centered care.

Learning Objectives:
The University of Texas MD Anderson Cancer Center participated in the Patient-Centered Outcomes Research (PCOR) ICU Collaborative through the Society of Critical Care Medicine. For this collaborative, we created the ICU Communication and Empowerment Project (ICE) to introduce a series of initiatives to promote family involvement in patient care while being sensitive to their values, cultural beliefs, and emotional well-being.

Methods:
A multidisciplinary team was created for facilitating information dissemination and implementing initiatives. Through our workgroup we instituted a visitor pass system, open visitation, and revamped the use of our two-way communication boards. We enhanced our waiting room experience by hosting ICU family centered events. Baseline (B) and Post Intervention (PI) family and clinician surveys were collected in the Rush University RedCap database.

Results:
There were 134 (B=79, PI=55) families and 127 (B=75, PI=52) clinicians participating in the surveys. The “good to excellent” average responses for family communications with ICU physicians and staff were B= 89.4% and PI=88%. The “good to excellent” average responses for family care and concern by ICU staff were B=90.9% and PI= 89%. Clinicians “strongly agree to somewhat agree” that having open visitation was beneficial for families (PI=64.3%). About half (50.9%) of the clinicians “strongly agree to somewhat agree” that communication with family members improved since the new two-way communication boards were implemented in the ICU.

Conclusion:
The SCCM PCOR Collaborative provided a platform for implementation of the ICE Project and effectively promoted patient and family centered care. Post intervention surveys showed that families remained happy with their ICU experience; however, the additional initiatives did not improve satisfaction significantly. This could be explained by an already high baseline interaction between families and our ICU staff, and/or inconsistent exposure to all interventions. Further work is needed to make these initiatives universally accessible in our practice.
ABSTRACT
Analysis of RSK Activity Following Serotonin Treatment

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Sponsored by: John H. Byrne, Ph.D., Department of Neurobiology and Anatomy
Supported by: John H. Byrne, Ph.D., Department of Neurobiology and Anatomy
Key Words: P90 ribosomal s6 kinase, Aplysia, Long-Term Facilitation

Background: The induction of long-term synaptic facilitation (LTF) in the mollusk Aplysia involves multiple signaling pathways, resulting in increased transcription of the CCAAT/enhancer-binding protein (C/EBP) gene, which is required for LTF. It has been proposed that the p90 ribosomal s6 kinase (RSK) phosphorylates and activates cyclic-AMP response element binding protein 1 (CREB1), thus promoting C/EBP expression and LTF. In humans, mutation of the RSK2 gene leads to Coffin-Lowry syndrome (CLS), resulting in cognitive deficits. My project aimed to validate a mammalian antibody to Aplysia phosphorylated RSK (pRSK), and subsequently use this antibody to measure pRSK levels at different time points post-treatment of serotonin (5-HT).

Methods: To validate the specificity of the mammalian antibody to Aplysia pRSK, protein lysates from Aplysia pleural-pedal ganglia were used for a Western blot, with dilutions of 1:500 for the primary antibody and 1:1000 for the secondary antibody in 5% dry nonfat milk. To determine whether the antibody is specific to phosphorylated RSK, a lambda phosphatase, applied at a concentration of 800 units, was used to pretreat lysate before antibody labeling to dephosphorylate pRSK. Following antibody validation, cultured Aplysia sensory neurons were either treated with five 5-minute 5-HT pulses to induce LTF, or with a vehicle solution. Neurons were fixed for immunostaining immediately post-treatment, or following 1, 5, or 24 hours post treatment. Cells were then incubated in 1:200 dilutions of pRSK primary antibody, followed by 1:200 dilutions of secondary antibodies. Immunofluorescence was then measured using a 63x Zeiss Confocal Microscope.

Results: Western blot analysis showed a single band around 90 kDa, which is the predicted molecular weight of pRSK. Also, no band was seen where pre-treated with the lambda phosphatase, thus confirming the specificity of the antibody to pRSK. Immunofluorescence analysis compared pRSK levels of 5-HT treated neurons normalized to the control group, fixed at the four previously mentioned time points, and suggested a delayed increase in pRSK after 5-HT (mean percentage control, ± SEM: 0 h, -0.17 ± 7.76%, n = 6; 1 h, -3.90 ± 3.60%, n = 2; 5 h, +24.81 ± 23.49%, n = 2; 24 h, +5.13 ± 7.29%, n = 4). However, a one-way ANOVA failed to show significance, possibly due to the small sample size. Further experiments will be needed to obtain a more accurate representation of the pRSK time course.
ABSTRACT

Changes in Retreatment Rates of Cerebral Aneurysms Over a 10-Year Period in a Population-Level Cohort

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Sponsored by: Sunil A. Sheth, MD, Department of Neurology
Supported by: University of Texas Rising STARs Award (PI: Sunil A. Sheth)
Key Words: Aneurysm, Endovascular treatment, Retreatment

Introduction: Prior studies have reported higher retreatment rates (RR) for cerebral aneurysms (CAs) after endovascular coiling (EC) compared to surgical clipping (SC). However, RRs have largely been derived from studies in the early 2000s and may not represent current practice.

Methods: Using administrative data on all discharges from acute care hospitals in California (2005-2011) and Florida (2005-2014), we identified patients with ruptured and unruptured CAs who were treated with EC or SC. Retreatments within 3 months were excluded, to minimize the inclusion of planned retreatments. Logistic regression was used to assess factors associated with retreatment, and results are presented as OR [95% CI].

Results: Among 19,650 patients with CAs, 12,441 (63.3%) were treated with EC and 7,209 (36.7%) with SC. Mean age was 57 ± 13, 72% were female and 12% were black. Between 2005 and 2014, the use of EC increased relative to SC (50% vs. 81%, p<0.0001). Retreatment occurred in 1488 (7.6%) patients (10.1% vs. 3.2%, EC vs. SC), with 89% within 2 years of index treatment. Retreatment was associated with age > 80 (OR 0.3 [0.2-0.5]), female sex (OR 1.6 [1.4-1.9]), black vs. white race (OR 0.8 [0.7-0.9]) and EC vs. SC (OR 3.5 [3.1-4.1]). Adjusted two-year RR decreased from 2005 to 2011 for patients with unruptured CAs treated with EC (8.7% vs. 6.8%, OR 0.95 [0.90-1.00] and Figure). Adjusted RR was unchanged for SC (mean RR 3.6% and 2.7%, unruptured and ruptured) and ruptured CAs treated with EC (mean RR 9.9%).

Conclusions: Analysis of two-year RR of CAs in a large real-world cohort demonstrates a continuous reduction in RR for unruptured CAs treated with EC in the last decade. These findings may reflect improving obliteration rates of EC for unruptured CAs.
ABSTRACT

Two Sides of the Same Coin:
Features of Oncometabolism Exposed in the Stressed Heart

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Sponsored by: Heinrich Taegtmeyer, MD, DPhil, Department of Internal Medicine
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases  
(2T35 DK007676-24)
Key Words: Warburg Effect, PKM2, lactate, heart muscle

Background: In 1924, Otto Warburg reported that cancer cells fermented glucose into lactate even when oxygen levels were sufficient for mitochondrial respiration. Although a definitive explanation of the Warburg effect has remained elusive, one hypothesis proposes that the Warburg effect results in the accumulation of glycolytic intermediaries that are then shifted towards biosynthetic pathways that sustain rapid cellular growth. Like cancer cells, cardiomyocytes also modify their metabolism in response to stress. When stressed, the heart remodels and reverts to the fetal gene program, which results in an increase in the expression of the fetal pyruvate kinase isoform (PKM2), which has decreased activity compared to the adult M1 isoform and increases lactate production. The lab recently found footprints of the Warburg effect in failing heart muscle, including an increase in expression of PKM2. Whether these glucose derived products support cardiac hypertrophy remains to be determined.

Hypothesis: Glucose metabolism provides the biosynthetic precursors for cardiomyocyte hypertrophy induced by B-adrenergic agents via the Warburg effect.

Methods: Adult mouse ventricular myocytes (AMVMs) were plated in RPMI supplemented with glucose (11mM), insulin, 0.4 mM oleate and 2% bovine serum albumin and supplemented with isoproterenol or phosphate buffered saline. These conditions were maintained for 48 hours. Cells were harvested and protein extracted for immunoblotting of PKM2 and coupled enzymatic assay for determination of intracellular G6P and extracellular lactate. To identify the fate of glucose-derived carbons, a pulse-chase experiment was performed and AMVMs were plated with U-14C glucose. DNA, RNA, proteins, and polar and aqueous fractions were separated and extracted and DPMs of each fraction were determined.

Results: Treatment with isoproterenol results in AMVM hypertrophy when glucose is present in the medium. AMVMs treated with 3OMG, a glucose analogue (which can be transported into the cell but is not phosphorylated or metabolized), do not hypertrophy in response to isoproterenol. Treatment with isoproterenol and glucose results in a significant increase in the amount of lactate produced by AMVMs, compared to those AMVMs that were treated with glucose without isoproterenol. There was no increase in the amount of G6P produced between the two groups. There was significantly less 14C enrichment in the proteins of AMVMs treated with isoproterenol. There is no significant difference in 14C enrichment in any of the other macromolecules (DNA, RNA, polar and aqueous fractions). Immunoblotting for PKM1/2 in these conditions has been inconclusive.

Conclusions: My results suggest that while glucose is necessary for hypertrophy, it does not provide the building blocks. Therefore, in cardiomyocytes, the Warburg effect plays a
different role than providing accumulation of biosynthetic precursors. I therefore propose that the increase in aerobic glycolysis may provide the necessary chemical energy or reducing equivalents used to support the hypertrophic process in cardiac myocytes.
ABSTRACT
Dissecting Stress Granules in Osteosarcoma-associated Chemoresistance by LFS iPSC Disease Model

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Sponsored by: Dung-Fang Lee, Ph.D., Department of Integrative Biology and Pharmacology
Supported by: Dung-Fang Lee, Ph.D., Department of Integrative Biology and Pharmacology
Key Words: iPSC, Stress Granules, Chemoresistance, LFS, Osteosarcoma

The emergence of induced pluripotent stem cells (iPSCs) has created a reliable and potentially infinite model for studying disease mechanisms in vitro. The iPSC model was used to model Li-Fraumeni Syndrome (LFS) osteosarcoma, and demonstrated the ability to recapitulate the features of osteosarcoma, including gene signature and tumorigenesis. LFS is characterized by germ-line mutations of the TP53 gene leading to a variety of early onset tumors, such as adolescent osteosarcoma. In addition, mutations in p53 have been shown to confer chemoresistance. Recently, it was shown that the upregulation of stress granules (SGs) in some cancer cell lines confers chemoresistance. Therefore, we expected that there is an increase in SG formation in p53 mutated osteosarcoma leading to increased chemoresistance. Our aim was to determine if there is an upregulation of SG formation in LFS iPSC-derived osteoblasts.

To test our hypothesis, we first established our methods using cancer cell lines previously used in studying KRAS-mediated SG formation. We determined that cells would be treated with 100µM sodium arsenate for one hour, and then stained for GTPase activating protein (SH3 domain) binding protein 1 (G3BP) to detect SG formation. After staining, the cells were viewed using an immunofluorescence microscope and images of the cells were recorded. This methodology was applied to each series of experiments. Next, LFS patient and WT family member derived iPSCs were maintained, cultured, treated and stained. Additionally, osteosarcoma cell lines (p53 WT line OSA and U2OS and p53 mutated line HOS and 143B) were studied using the same methods. Finally, we used lentivirus-carrying different mutant p53 to modify cellular p53 status in osteosarcoma cell lines. Viral packaging plasmids and mutant p53 or WT p53/control plasmids were transfected into 293T cells in order to produce lentiviral practices to infect the WT p53 osteosarcoma cell lines OSA and U20S. The infected osteosarcoma cells were then treated and stained. The recorded images of all the stained cells were analyzed for the SG area inside the area of the cell, which is referred to as the SG index.

While our initial experiment proved our ability to induce SG formation and document the results, our results did not support our hypothesis. SG formation in LFS and WT iPSC derived osteoblasts showed SG formation that was not dependent on p53 mutation status. Only one of three mutated LFS derived osteoblast groups produced SG formation, while one of the two WT p53 osteoblast groups also produced SG. While both mutated p53 cell lines demonstrated stress granule formation, the WT p53 line, U2OS, showed the most SG formation. Finally, we ectopically expressed mutant p53 in WT p53 lines. Contrary to our expectation, there was no difference between cells ectopically expressing either mutated or WT p53. Thus, these findings do not support our original hypothesis that increased chemoresistance in LFS osteosarcoma is due to
the formation of SGs. In summary, our results indicate SG formation is independent of mutated p53 status, thus the differences in SG formation must be due to another unknown mechanism not studied in these experiments.
ABSTRACT

Association of perioperative opioid use and esophageal cancer recurrence: a retrospective study

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Sponsored by: Dr. Juan Cata, MD, MD Anderson Department of Perioperative Medicine and Anesthesia

Supported by: MD Anderson Department of Anesthesiology, Critical Care, & Pain Medicine

Key Words: Anesthesiology, perioperative medicine, opioids, esophageal cancer

Background: Opioids are the most commonly prescribed analgesia in perioperative cancer care and pain management. However, recent experimental and clinical studies raise concern that differences in anesthetic regimens may play a role in oncological survival rates. Specifically, it has been suggested that use of opioids could modulate prognostic factors that impact cancer recurrence. The effects of intraoperative opioid use on esophageal cancer have only been addressed by a few reports. This study aims to investigate whether the use of opioid in the perioperative period plays a role on the incidence of recurrence-free survival and overall survival in patients with non-metastatic esophageal cancer.

Methods: We retrieved data on opioid on 773 patients with non-metastatic esophageal cancer who underwent surgery at the Texas MD Anderson Cancer Center. Patient data was grouped based on low or high levels of intraoperative morphine equivalent dosage (MEDD) (Recursive PARTitioning [rpart] cutoff = 710 MEDD). Kaplan-Meier analyses and Cox proportional analyses were conducted to assess the association between intraoperative morphine equivalent dosage (MEDD) on recurrence-free survival (RFS) and overall survival (OS).

Results: Kaplan-Meier analyses indicated that lower MEDD (<710) was significantly associated with reduced recurrence-free survival (p = 0.0389) and marginally significant for poorer overall survival (p= 0.0784). With the adjustment of age, BMI, stage, histology, pre-operative chemotherapy, and post-operative chemotherapy, multivariate analysis indicated a significant association between the level of intraoperative MEDD (<710 vs. ≥710) and RFS (p-value=0.0165; HR=1.312, 95% CI: 1.051~1.638). Likewise, with the adjustment of age, BMI, stage, histology, preoperative chemotherapy, and postoperative chemotherapy, multivariate analysis indicated marginal significance in association between the level of intraoperative MEDD (<710 vs. ≥ 710) and OS (p-value=0.0994; HR=1.221, 95% CI: 0.963~1.547).

Conclusion: The results of this study indicate that the level of intraoperative opioids use may play a role in esophageal cancer recurrence and overall survival. However, we recognize that the retrospective nature of this clinical study may be influenced by confounding or unmeasured factors. Until randomized controlled studies explore this association further, opioids should continue to be a key component of balanced anesthesia in patients with esophageal cancer.
ABSTRACT

The Association of Adipocytokines with Insulin Resistance, Inflammation and Atherosclerosis in a Mexican-American Border Population

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Sponsored by: Absalon Gutierrez, MD, Division of Endocrinology, Diabetes, and Metabolism

Supported by: NIH NIDDK, 5T35DK007676-24

Key Words: Adipocytokines, cIMT, Diabetes Mellitus, Atherosclerosis, Mexican-American

Background: Leptin, resistin, and adiponectin are adipocytokines - hormones secreted from adipose tissue - which influence insulin resistance and atherosclerosis. Leptin increases energy expenditure and suppresses appetite. Resistin increases inflammation and vascular dysfunction. Adiponectin promotes anti-inflammatory mechanisms and whole body insulin sensitization. Mixed-population studies suggest that worsening insulin resistance is associated with higher levels of leptin and resistin, and with lower levels of adiponectin.

Significance: In Hispanic populations, the levels of three key adipocytokines - leptin, resistin and adiponectin - are unknown across various levels of insulin resistance. The relationship of these levels to carotid intima thickness (cIMT) – a marker of atherosclerosis - is also unknown.

Hypotheses: 1) In a Mexican-American population, increasing levels of leptin and resistin – as well as decreased levels of adiponectin – are associated with the increasing severity of insulin resistance and inflammation, 2) In a Mexican-American population, increased imaging evidence of atherosclerosis (via cIMT) is seen across rising levels of insulin resistance.

Experimental Design: Human subjects from the Cameron County Hispanic Cohort were studied via retrospective cross sectional analysis and stratified into three groups of insulin resistance (nondiabetic, prediabetic, and diabetes mellitus). The final study database only included subjects with measurements of aforementioned cytokines. Subjects were excluded based on age < 18 years old, tobacco use, pregnancy, active malignancy, major adverse cardiovascular events, and confounding medications (statins and relevant antihyperglycemic medications). There were 819 subjects (43%, 35% and 22% for nondiabetics, prediabetics and diabetics, respectively) for the study of adipocytokines and 249 subjects for the study of cIMT (34%, 50% and 16% for nondiabetics, prediabetics and diabetics, respectively).

Results/Data: Across the groups, univariable analysis (of log transformed values) showed significantly different levels of leptin (p<0.001), levels approaching significance for adiponectin (p=0.057), and no significant differences for resistin (p=0.1). After controlling for gender, hypertension, age, and BMI, adiponectin levels lowered significantly across increasing levels of insulin resistance (p=0.002) and resistin levels did not change significantly across groups (p=0.10). Compared to nondiabetics, leptin levels surprisingly decreased significantly among diabetics (p=0.013), while prediabetics had higher leptin levels than those among nondiabetics (p=0.011). cIMT levels heightened across intensifying insulin resistance (p=0.01).

Conclusion: In a Mexican-American population, diabetic subjects had lower levels of leptin compared to nondiabetics, which is contrary to our hypothesis. This argues for the presence of leptin deficiency, rather than the usual mechanism of leptin resistance, in this population of diabetic subjects. Also contrary to our hypothesis was the lack of change in resistin. As expected,
adiponectin levels decreased across groups and cIMT measurement increased across groups. These findings support more research on the role of leptin deficiency and diabetes in this population. The relationship of resistin to insulin resistance also merits further study.
ABSTRACT
Patient Reported Outcomes Following Sever Chest Injury

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Sponsored by:  Dr. John Harvin, M.D., Charles E Wade, PhD
Supported by:  McGovern Medical School Department of Surgery; CeTIR
Key Words:  Sever chest injury, patient centered, patient reported

Introduction: Patient reported outcomes following injury are lacking. The National Institutes of Health and American College of Surgeons have called for the need to implement more patient centered methods in collecting post-discharge outcomes from large trauma registries.\textsuperscript{1} Chest injury is a common cause of mortality and morbidity.\textsuperscript{ii,iii,iv} We aim to better characterize short-term patient reported outcomes following severe chest injury.

Methods: After IRB approval, we conducted a prospective observational study from June 3, 2017 through August 5, 2017. Patients admitted to the Memorial Hermann Hospital-Texas Medical Center trauma services following blunt injury were screened for severe chest injury, defined as flail chest, ≥6 consecutive rib fractures, or ≥1 displaced rib fracture. Patients with spinal cord injury, preexisting cardiac/pulmonary disease, or bilateral LE non weight bearing fractures were excluded. In patients who consented, health status was assessed using the EuroQol-5D(5L) form and quality of life the standard gamble.

Results: Over the study period, 626 patients were screened and 42 patients met inclusion criteria. Twenty-two patients either did not consent or had an exclusion criteria, leaving 20 enrolled patients. The patients had a mean age of 45 years (SD 17) and were severely injured (mean Injury Severity Score 22 [SD 12]). The majority of rib fracture patterns included were ≥6 consecutive rib fractures (14 or 70%), followed by ≥1 displaced rib fracture (5 or 25%), and flail chest (1 or 5%). The mean EuroQol-5D(5L) visual analogue scale (overall health status) was 0.70 (SD 24); the mean visual analogue scale for patients in the United States is 80 (SD not known). The mean utility as measured by the standard gamble was 0.75 (SD 0.35). The EuroQOL-5D(5L) domains are shown below:

Conclusion: In this group of injured patients, severe chest injury resulted in a reduction of overall health status and quality of life. The domains with the lowest reported health status were usual activities and self care. This study is limited by unknown population norms for this group of patients. Future study will include a 6 month follow up to assess resolution of impaired health status and quality of life.
Mean Scores for EuroQOL-5D Domains

![Bar chart showing mean scores for various domains: Mobility Self-Care, Usual Activities, Pain, Anxiety. The chart includes error bars indicating variability.](chart.png)
ABSTRACT
Let the Right One In: High Admission Rate for Low Acuity Pediatric Burns

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Sponsored by: Kuojen Tsao MD, Pediatric Surgery
Supported by: Kuojen Tsao MD, Pediatric Surgery
Key Words: Pediatric Surgery, Burns


Introduction: More than 125,000 children present to Emergency Departments (ED) in the US every year, with less than 10% admitted for treatment. Many pediatric burns are minor and may be triaged in the Emergency Department (ED) with appropriate follow-up. The purpose of this study was to describe the status of emergency pediatric burn care triage to identify targets for value and quality improvement.

Methods: A retrospective record review of pediatric patients (<18 years) with primary burn injuries who presented to a tertiary, academic children’s emergency department in 2016 was conducted. Demographics, triage patterns, and injury characteristics such as total body surface area (TBSA) % burn were evaluated. Patients who were transferred to a burn specialty center for large burns (>30% TBSA) were excluded. Observation admission were those admitted to the hospital for less than 24 hours. Complications included graft failure, infection and ED revisit or readmission. Descriptive statistics, chi², and Wilcoxon rank sum tests were used for analysis. Multivariate logistic regression was used to evaluate the association of observation admission versus discharge from the ED.

Results: In 2016, 300 pediatric burn patients were triaged in the ED, with only 4 requiring transfer to a higher-level burn specialty center. Patients were typically young (median age 3.2 years, IQR 1.3-7.3), male (n=173, 58.5%), non-White Hispanic (n=135, 46.2%), and publically insured (n=226, 76.4%). The majority of patients were transferred from outside facilities (n=189, 63.9%) and arrived by ambulance (n=219, 74.2%). Scalding was the mechanism of injury for most children (n=166, 58.5%), followed by flame (n=49, 17.3%) and contact thermal injuries (n=46, 16.2%). Though most burns were small, not severe, and able to be debrided without sedation, the majority were admitted (n=235, 79.4%). In those admitted, length of stay was brief (median 1.5 days, IQR 1.9-3.9) with 36% admitted for less than 24 hours. There were few complications overall (n=12, 4.1%) and no difference in those admitted or discharged (p=0.27). Patient demographics, except for gender in patients admitted for less than 24 hours, were not associated with admission or discharge. Presentation after regular hours (07:00-19:00) but not day of the week, was
associated with observation admission. After adjusting for gender, method of arrival, transfer status, mechanism of injury, complexity, debridement requiring sedation, time of presentation and TBSA, only arrival by ambulance was associated with observation admission hours versus discharge from the ED.

**Conclusion:** Though most burns were low acuity, the majority of children were admitted. There may be an opportunity for improved resource utilization through standardized admission criteria and discharge protocols.
ABSTRACT
Cross-talk between the gut and the brain in rats subjected to LPS-induced inflammation: Role of α-synuclein.

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Sponsored by: Marie-Francoise Doursout, PhD, Department of Anesthesiology
Supported by: McGovern Medical School at UTHealth – Office of the Dean, Marie-Francoise Doursout, PhD, Department of Anesthesiology
Key Words: Parkinson’s, Gut-Brain-Axis, α-synuclein

Background: It is well established that the involvement of the gastrointestinal tract is of great interest as a contributing factor to the development and progression of neurodegenerative diseases. The dysregulation of the Gut-Brain-Axis (GBA) may be associated with gastrointestinal manifestations preceding disorders of cognitive and/or memory and learning process, supporting the hypothesis that the pathological process is spread from the gut to the brain. The extensive involvement of the gut in neurodegenerative diseases such as Parkinson’s disease, even in its early stages, has led to the evaluation of enteric α-synuclein as a possible biomarker. Therefore, the overall goal of the proposed study is to assess the time course of the compromised intestinal barrier capable of influencing brain function in rats challenged with LPS.

Hypothesis: Specifically, we hypothesize that alterations of the intestinal barrier (or leaky guts) enhances inflammation as well as the production of a unique protein α-synuclein which is characteristic of degenerative diseases.

Experimental Design: To induce inflammation, Lipopolysaccharide (LPS) was administered intravenously (IV) in rats at a dose of 20 mg/kg. A single dose LPS was elected based on previously reported results from a mouse model. Animals were divided into 2 groups (saline and 20 mg/kg LPS). Animals were also divided into 2 sub-groups (short term; 1 week and long term; 4 weeks). Following sacrifice at each time point tissues from the gut and brain (e.g. hippocampus and olfactory bulb) were harvested. We measured edema formation in the gut in rats subjected to LPS as compared to saline by wet/dry ratio. α-synuclein in the collected tissues was determined using ELISA (R&D Systems) at each time point. Protein concentration in each sample will be measured using a BCA protein assay kit. Data was analyzed by a one-way analysis of variance (ANOVA) to assess overall significance. When differences are significant, multiple within-comparisons were performed using Dunnett’s t-test. When changes are significant, the magnitude of changes in each experimental condition were compared using an unpaired t-test where p <0.05 was considered significant. Data is expressed as Mean ± SEM.

Results: Our data shows that LPS induced edema in the gut, suggesting inflammation. Although not yet finalized in the gut, our data demonstrates that increases in α-synuclein protein concentrations were time-dependent in the hippocampus.

Conclusion: We demonstrated that LPS challenge in rats induces edema in the gut. We also demonstrated increases in α-synuclein in the hippocampus in a time dependent manner. Currently, we are assessing increased α-synuclein in the olfactory bulb and gut to further understand the time course of deposition along the GBA and IL-6 in the plasma as in indicator
of inflammation. We postulate that LPS induces an increase in α-synuclein concentrations in the gut and later spreads to the brain. Our ultimate goal is to reach an understanding between the gut and brain interactions to further locate effective therapeutic regimens to treat or prevent related neurodegenerative diseases.
ABSTRACT

Analysis of the Effects of Acute Blood Glucose Levels on Complications Incurred Following a Traumatic Injury in Patients with Diabetes Mellitus

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McGovern Medical School at UTHealth

Class of 2020

Sponsored by: Center for Translational Injury Research
Supported by: Dr. Charles E. Wade
Key Words: diabetes mellitus, trauma, HbA1c, complications, hyperglycemia

Introduction: Diabetes is a chronic disorder that affects more than 30 million Americans today. Approximately 25% of patients admitted to the hospital have diagnosed diabetes mellitus and nearly a third of patients with the disorder are undiagnosed. The prevalence of diabetes has incited extensive research that suggests patients with diabetes mellitus specifically are at an increased risk for traumatic injuries. Studies have shown that the disorder is associated with longer stays in the ICU, more days on ventilator support, higher rates of infections and other complications after trauma. However, other studies have shown that there are no differences between diabetic and nondiabetic trauma patients when comparing hospital length of stay, mortality, risk for deep infection or DVTs. We believe these conflicting results may be due to similarities between controlled diabetics and nondiabetics suggesting further analysis of the diabetic population is required. We hypothesized that patients who experience acute abnormal glucose levels, as indicated by random blood sugar and HbA1c levels upon hospital admission, will have an increased risk for complications and mortality.

Methods and Aims: We conducted a retrospective analysis of level I trauma patients admitted to the surgical trauma intensive care unit (STICU) at Memorial Hermann Hospital between the years 2011-2016. Patients were in the STICU for >7 days, >15 years old, non-obstetric and non-prisoners. Patients diagnosed with diabetes mellitus II prior to trauma were divided into two groups based on their HbA1c levels. Those with HbA1c < 6.5 were placed in the controlled diabetic group and those with HbA1c > 6.5 were placed in the uncontrolled diabetic group. Nondiabetic patients were divided into hyperglycemic (≥ 200 mg/dL) and euglycemic (< 200 mg/dL) groups. For continuous and count variables, we used the Kruskal Wallis test and the Pearson’s chi-squared test to assess associations between categorical variables. Poisson regression was used to assess the effect of diabetic category on complication rates after adjusting for injury severity score (ISS), age, race, ethnicity, trauma type, base excess, AIS-head and length of stay.

Results: During this study, 258 trauma patients were evaluated. Of the 83 diabetics, 51 had demographics, HbA1c and comorbidities recorded. 175 of the 175 nondiabetics had demographics, blood glucose and comorbidities recorded. Uncontrolled diabetics did not have a significant difference in complication rates when compared to controlled diabetic, nondiabetic hyperglycemic and nondiabetic euglycemic patients.
Conclusion: DM is a prevalent disorder among trauma patients and is associated with many complications. Uncontrolled diabetes has the potential to induce comorbidities. Further research is required to properly compare complication rates between diabetic groups.
ABSTRACT

Renal Presentation of Tuberous Sclerosis Complex

INA GROSE
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Sponsored by: Joshua Samuels, MD, MPH, Pediatric Nephrology and Hypertension
Supported by: Joshua Samuels, MD, MPH, Pediatric Nephrology and Hypertension

Key Words: Tuberous sclerosis, Afinitor (everolimus), Renal

BACKGROUND: Tuberous Sclerosis Complex (TSC) occurs in 1 out of 5,000-10,000 live births (1). TSC is an autosomal dominant disorder, presenting with loss-of-function mutations in TSC1 and/or TSC2 genes. The majority of individuals with TSC present with loss-of-function mutations in TSC1 and/or TSC2 genes. TSC1 encodes for the protein hamartin, expressed in most adult tissues. While the specific function is unknown, hamartin forms and stabilizes a complex with tuberin, the gene product of TSC2 (2). Tuberin is a protein that is ubiquitously expressed in all adult tissues. Tuberin contains a gene region that is homologous with the catalytic domain of Rap1GAP, a GTPase-activating protein that downregulates Rap1 protein. Rap1 acts as a GTPase to induce DNA synthesis (3). A loss of function mutation of tuberin leads to activation of Rap1, leading to elevated signaling for DNA synthesis and cell growth. The hamartin-tuberin complex inhibits cellular signaling mediated by the mechanistic target of rapamycin (mTOR). mTOR functions to regulate protein translation and cell cycle progression. In TSC, downstream modulators of mTOR become unregulated, leading to unchecked tumor growth (2). The presentation of TSC is variable in age of symptomatic onset, tumor location, and tumor growth. The tumors that arise are benign hamartomas that present within the brain, skin, eyes, kidneys, and liver. Kidney lesions occur at a later onset but ultimately affect a majority (80%) of TSC patients (5). Renal manifestations of TSC most commonly present as angiomyolipomas (AMLs). Less commonly, benign cysts and renal cell carcinoma may occur. Progressive growth of AMLs within the kidney can lead to hemorrhage and interference with renal function, putting patients at risk for chronic kidney disease (6).

METHODS: We created a quality improvement-centered patient database highlighting the variable presentations of TSC to identify demographic and clinical variables that affect renal prognosis and management of TSC. Patient age, mutation phenotype, and renal lesion character were recorded to observe how these parameters affected renal lesion size and renal function. Additionally, the treatment of renal lesions, either with Afinitor (everolimus) or anti-hypertensives were recorded to determine if drug therapy led to improved prognosis of patients with TSC.

RESULTS: The established database included 256 total patients, where all patients who attended the TSC Center of Excellence in Houston, TX between September 2001 and July 2017 were eligible for consideration. Patients were predominately female (n=139, 54%), white (n=215, 84%) with 20% (n=52) of Hispanic identity. Although 43% of patients did not have genotyping done, TSC2 mutations were the most common genotype (n=102, 40%) followed by TSC 1 (9%) and no mutation identified (8%). Concerning TSC treatment, 40 (19%) of patients were given Afinitor and 32 (13%) of patients were given anti-hypertensive medications. Imaging procedures were performed on 124 patients, where MRI was the most common imaging modality (48%). The renal imaging reports identified AML in 94 patients (37%), cysts in 109 patients (43%), followed by carcinoma (1%) and other lesions (8%). Based on the preliminary outcomes, the...
anticipated prevalence of TSC increases with an association with the female gender and increased age of symptomatic onset. Patients with TSC2 mutations will have a greater manifestation of lesions compared to other genotypes (7).

Resources:


ABSTRACT

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9)’s Role in Autophagy

SAXON HANCOCK McGovern Medical School at UTHealth Class of 2020

Sponsored by: Ba-Bie Teng, PhD, Center for Human Genetics, The Brown Foundation Institute of Molecular Medicine

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5T35DK007676-24

Key Words: PCSK9, atherosclerosis, autophagy

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) is a multifaceted protein best known for its role in degrading the low-density lipoprotein receptor (LDLR), making it a significant therapeutic target for atherosclerotic disease. A number of PCSK9 inhibitors have been released for patients whose cholesterol levels cannot be controlled on statins alone, however, PCSK9 has other complex interactions which remain to be elucidated. Previous work suggests that PCSK9 is involved in an autophagic process which regulates lipoprotein ApoB independently of the LDLR. PCSK9 also is found in the brain, where it is not fully understood, but is involved in a variety of processes such as neuronal apoptosis, stroke, and traumatic brain injury.

In order to further understand PCSK9’s role in liver and brain lipid metabolism and autophagy, previously generated siRNA, microRNAs (miRNAs) -601 and -632, and CRISPR/CAS9 RNA targeted against PCSK9 are to be transfected via the lipofectamine 2000 vector into HepG2 and U87 cells. At 48 hours post transfection the media is to be collected and cell lysate is to be extracted of protein and RNA. SDS/Page and subsequent western blotting will be performed on samples in order to observe relevant protein expression levels and qPCR will be run in order to quantify mRNA expression of PCSK9. We will examine LDL uptake in PCSK9 inhibited cells by incubating cells with fluorescent Di-LDL. Expected results are that PCSK9 will have lower expression which will lead to increased LDLR expression, decreased ApoB levels, and decreased low-density lipoprotein levels. In addition, novel observations of proteins involved in the autophagy pathway such as Akt, AMPK, ULK-1, Beclin-1, and Atg14L are expected in the liver and brain. Finishing this study will take future efforts to complete the data set. It holds high promise in further elucidating PCSK9’s role in autophagy and lipid metabolism both in the liver and brain. Understanding PCSK9’s mechanisms fully is critical to provide new therapeutic targets and give insight into potential side effects of its inhibition.
ABSTRACT

Exploring the family financial burden of outpatient pediatric surgical care and interest in telemedicine for post-operative care

KAILEY HARRIS

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Sponsored by: Mary T. Austin, MD, MPH, Department of Pediatric Surgery
Supported by: Mary T. Austin, MD, MPH, Department of Pediatric Surgery; McGovern Medical School – Office of the Dean

Key Words: telemedicine, pediatric surgery, clinic, cost

Introduction: Telemedicine has the potential to decrease the financial burden of postoperative outpatient care for families of pediatric surgical patients. The purpose of this study was to determine travel and work-related costs related to pediatric surgical clinic visits and parents' attitudes towards utilizing telemedicine.

Methods: A non-random sample comprised of parents of patients presenting to our outpatient pediatric surgery clinic for postoperative, preoperative, and new consults were administered a previously published 29-question survey that aimed to assess the burden of attending clinic, while also querying their preferences towards telemedicine for postoperative care. Pearson chi-square test and univariate logistic regression were used for statistical analysis.

Results: Among 186 survey respondents, most were Hispanic (n=125) followed by non-Hispanic white (NHW) (n=31), non-Hispanic black (NHB) (n=14) and 16 other/unknown. Eighty-one (44%) parents traveled < 25 miles, 78 (43%) traveled between 26-50 miles, and 24 (13%) traveled > 50 miles. The majority of respondents (n=58, 33%) spent $25 to $50 on travel and additional ancillary expenses. Regarding telemedicine in the form of video conferencing for postoperative care, most parents were comfortable using telemedicine to discuss general questions that arose (n=122, 75%) and for routine follow-up (n=94, 56%). Fewer parents were comfortable with the use of telemedicine to assess acute problems (n=72, 45%). Comfort in using telemedicine for postoperative care was not associated with perceived total costs, distance traveled, education level, income level, race, or age. The strongest predictor for comfort in using telemedicine for postoperative care was being comfortable communicating by email and/or telemedicine to discuss medical issues. Spanish-only speaking parents were significantly more likely than English speaking parents to be comfortable using telemedicine for routine postoperative follow-up (OR 2.17; 95% CI 1.01-4.61). There was no significant difference between Spanish-only speaking parents and English-speaking parents when assessing comfort with using telemedicine for acute problems (OR 1.7; 95% CI 0.79-3.65) or general questions (OR 0.88; 95% CI 0.38-2.02).

Conclusion: Clinic visits result in significant costs for parents of pediatric surgical patients. Overall, comfort in using communication technologies was the strongest predictor for comfort using telemedicine for postoperative care. Spanish-only speaking parents were more likely to
be comfortable using telemedicine for routine postoperative follow-up as compared to English-speaking parents.
**ABSTRACT**

Mathematical Modeling of Tumor Response to Ipilimumab Therapy

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Sponsored by:  
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Supported by:  
Vittorio Cristini; McGovern Medical School SRP

Key Words:  
Immunotherapy; mathematical modeling; cancer

Immunotherapy has proven to be a novel approach in the treatment of various cancer types; it expounds upon the strength of one’s own immune system. However, inter-patient and inter-tumor heterogeneity is highly relevant in the case of immunotherapy response: drugs like ipilimumab drive significant improvement in some patients while proving to be futile in others. The complex growth kinetics of each tumor, as well as the “innate strength” of the patients’ immune system, can cause dramatic variances in tumor response to ipilimumab therapy. It is crucial to create a robust mathematical model that can quantify these patient responses to ipilimumab and other immunotherapies in order to understand tumor growth and predicting patient response to therapy.

We incorporated three basic parameters ($\alpha$, $\Lambda$, and $\mu$) in the mathematical model to predict tumor response over time. We used a nonlinear differential equation for tumor mass over time:

$$\frac{dp}{dt} = \alpha p - p[1 + \Lambda(p - 1)]\mu$$  \hspace{1cm} (S1)

where $p$ is the dimensionless tumor mass (ratio of tumor mass over initial tumor mass); $\alpha$ is the proliferation rate of tumor growth in absence of treatment [s$^{-1}$], $\Lambda$ is an abstract term that depends on the number of immune cells required to kill one tumor cell and the ratio between initial tumor mass and immune cell count, and $\mu$ is the efficacy of the immunotherapy treatment in activating immune cells [s$^{-1}$].
ABSTRACT
Quantifying the Physiologic Effects of Neoadjuvant Chemoradiation on Patients with Carcinoma of the Esophagus by Integrative Cardiopulmonary Exercise Testing (CPET)

EMILY HENDERSON  
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Sponsored by: Anh Q. Dang, MD, Department of Anesthesiology & Perioperative Medicine, University of Texas M.D. Anderson Cancer Center, Houston, Texas

Supported by: Bernhard Riedel, MD; Shital Vachhani, MD; Benjamin Arnold, MD; January Tsai, MD; Teresa Moon, MD; Jonathan Wilks, MD; Curtis Hightower, MD; Mike Hernandez, MS

Key Words: CPET, Esophagectomy, Cardiotoxicity, Post-Surgery

Background: Esophageal carcinoma patients are commonly placed on a multimodal treatment regimen that includes chemoradiation and surgery. However, the high number of side effects associated with chemoradiation can be detrimental to cardiopulmonary physiology. In the past a patient’s physiologic status following therapy has been measured using single organ assessments such as electrocardiogram and pulmonary function tests. However, CPET is now being used to more accurately integrate the cardiorespiratory and skeletal muscle systems. This study aims to use CPET to determine the effects of chemoradiation on the pathophysiologic state of esophageal carcinoma patients.

Methods: Eight patients underwent CPET prior to neoadjuvant chemoradiation therapy and again following therapy. CPET analysis was performed using cycle ergometer (pedaling at 60 rpm, 15-25 w/minute ramp protocol). Statistical analysis included paired students t-test and post hoc Bonferroni corrections.

Results: The heart rate at peak exercise, hemoglobin, weight, and respiratory function tests (minute ventilation, maximal forced expiratory and inspiratory flow rates) were unchanged following neoadjuvant chemoradiation. There was an increase in the baseline heart rate following neoadjuvant therapy from $65 \pm 11$ to $75 \pm 13$ beats per minute ($p=0.05$). There was a significant decrease in both the % predicted anaerobic threshold from $88 \pm 14$ to $74 \pm 6$ ($p=0.01$) and % predicted peak oxygen consumption from $81 \pm 11$ to $71 \pm 9$ ($p<0.0001$). There was a significant decrease in $\Delta VO_2/\Delta WR$, a predictor of cardiac output, from $10.1 \pm 1$ to $9.0 \pm 1$ following neoadjuvant therapy ($p=0.0013$). Oxygen pulse, a predictor of stroke volume, was significantly decreased for unloaded cycling, AT, and peak exercise ($p=0.02$).

Conclusion: These data suggest that neoadjuvant chemoradiation in patients with esophageal carcinoma lead to acute cardiotoxicity without detriment to respiratory function. For future research, CPET can be used to assess physical status in patients with esophageal carcinoma who undergo neoadjuvant chemoradiation to determine whether these measures correlate with postsurgical complications.
ABSTRACT

The Pharmacokinetic Effects of Fucoidan on Chemotherapeutic Regimens

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Sponsored by:  Judith A. Smith, B.S. Pharm.D., BCOP, CPHQ, FCCP, FISOPP, Department of Obstetrics, Gynecology, and Reproductive Sciences

Supported by:  Judith A. Smith, Pharm.D., BCOP, CPHQ, FCCP, FISOPP

Key Words:  Fucoidan, cancer, chemotherapy, pharmacokinetics

Background:  Fucoidan is a polysaccharide that is extracted from certain species of brown seaweed and marine invertebrates. Preclinical studies have indicated that fucoidan may exhibit antitumor and immunomodulatory properties that can benefit cancer patients. Before such bioactive properties can be investigated, this study sought to identify potential interactions between fucoidan and chemotherapeutic regimens, as well as to determine if supplementation alters chemotherapy pharmacokinetics. Fucoidan has extremely limited bioavailability when administered as an oral supplement, therefore, the supplement would have little to negligible pharmacokinetic effects on chemotherapy.

Methods:  This study will compare the pharmacokinetics and adverse effects of selected chemotherapy regimens alone to the same parameters with fucoidan supplementation. A total of ten patients receiving paclitaxel with carboplatin and ten patients receiving 5-fluorouracil with Oxaliplatin (FOLFOX) at the Memorial Hermann Cancer Center. Study subjects were randomized to take fucoidan supplements before Cycle 1 or Cycle 2 of chemotherapy. Pharmacokinetic blood samples were collected during these infusions and analyzed. Toxicity and compliance with regular supplementation were also monitored over the course of patient participation in this study.

Results:  This study is ongoing with anticipated enrollment to conclude in October 2017. To date, four patients on the paclitaxel-carboplatin regimen and two patients on the FOLFOX regimen have been enrolled. Toxicities and adverse effects are actively monitored during chemotherapy cycles with and without fucoidan, and, thus far, no differences in adverse effects attributed to chemotherapy have been observed. Analyses of potential differences in pharmacokinetic profiles of chemotherapeutic agents with and without fucoidan supplementation are ongoing and will be presented during a poster session.

Conclusion:  Future studies should evaluate the bioactive properties of fucoidan in cancer patients to further elucidate its potential benefit as an adjunct to chemotherapy. Hopefully, this initial pharmacokinetic evaluation will encourage future study of the benefits of fucoidan for cancer patients and its potential to improve quality of life and health outcomes.
ABSTRACT

Impact of Fibrinolytic Phenotype on Outcomes in Thermally-Injured Patients

VICTORIA HOELSCHER  McGovern Medical School at UTHealth  Class of 2020

Sponsored by: Bryan A Cotton, MD, Charles E Wade, PhD, Todd F Huzar, MD
Supported by: McGovern Medical School Department of Surgery; CeTIR
Key Words: Fibrinolysis shutdown, hyperfibrinolysis, burns, thromboelastography

Introduction: Fibrinolysis is the physiologic destruction of fibrin clots following their formation that serves to keep microvasculature open and functional. Both extremes of this process, hyperfibrinolysis and fibrinolysis shutdown respectively, have been associated with increased mortality in both adult and pediatric trauma populations. We hypothesized that these fibrinolytic phenotypes occur in patients with thermal injuries and are associated with increased resuscitation volumes, complications, and mortality.

Methods: A retrospective analysis was performed on patients admitted to the John S Dunn Burn Center at Memorial Hermann between 01/2009 and 12/2016 with age ≥ 18 years, TBSA ≥ 20%, and a survival ≥ 24 hours post admission. Patients were first divided into three groups representing their fibrinolytic states using a quantitative indicator of percent clot lysis at 30 minutes (LY30) determined by thromboelastography. LY30 ≤ 0.9% indicates fibrinolysis shutdown (SD), 0.9% to 2.9%, physiologic fibrinolysis (PHYS), and ≥ 3%, hyperfibrinolysis (HF). Univariate and multivariate analyses were performed.

Results: Of 145 patients who met the inclusion criteria, 48% presented with SD while 36% presented with PHYS and 16% with HF. Both SD and HF patients had higher base deficits than those with PHYS [(median 9 (6, 2) and 8 (7, 2) vs. 3 (6, 1); p = 0.006]) and received more fluids during 24-hour resuscitation [(median 3.3mL/kg/TBSA (2.4, 4.3) and 3.5 (2.9, 4.4) versus 2.6 (2.1, 3.6); p = 0.008)]. While there was a trend towards higher mortality and occurrence of sepsis and respiratory failure in patients with SD (versus PHYS or HF), this was not statistically significant. (TABLE) When controlling for age, gender, %TBSA, and inhalation injury, SD patients were 3.5 times more likely to experience in-hospital mortality than patients presenting with the PHYS or HF phenotypes (OR 3.56, 95% C.I. p = 0.031).

Conclusions: In severely burned patients, shutdown is the most common fibrinolytic phenotype and is associated with a three and a half-fold increased risk of mortality. Shutdown patients also appear more likely to develop respiratory failure and sepsis compared to physiologic and hyperfibrinolytic patients.

<table>
<thead>
<tr>
<th></th>
<th>Shutdown (n=69)</th>
<th>Physiologic (n=52)</th>
<th>Hyper (n=24)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>30%</td>
<td>21%</td>
<td>17%</td>
<td>0.190</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>32%</td>
<td>21%</td>
<td>13%</td>
<td>0.065</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>49%</td>
<td>32%</td>
<td>50%</td>
<td>0.067</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>39%</td>
<td>23%</td>
<td>29%</td>
<td>0.061</td>
</tr>
</tbody>
</table>

TABLE: Comparison of outcomes between fibrinolytic phenotypes.
ABSTRACT

Safety of robotic assisted laparoscopic recurrent paraesophageal hernia repair: Insights from a large single institution experience

Nicholas F. Holton
McGovern Medical School at UTHealth

Background: Laparoscopic repair of recurrent as opposed to primary paraesophageal hernias (PEH) are associated with increased peri-operative complication rates, worse outcomes, and increased conversion rates. The robotic platform may aid surgeons in these complex revisional procedures. Our aim was to compare the outcomes of patients undergoing robotic assisted laparoscopic (RAL) repair of recurrent as opposed to primary PEHs.

Methods: Patients undergoing RAL primary and recurrent PEH repairs from 2009-2017 performed at a single institution were reviewed. Demographics, use of mesh, estimated blood loss, intra-operative complications, conversion rates, operative time, rates of esophageal/gastric leak, hospital length of stay, readmission/re-operation rates, recurrence, dysphagia, gas bloat, and pre- and post-operative proton pump inhibitor (PPI) use were analyzed. Analysis was performed using the appropriate parametric or non-parametric analysis (continuous data) or Pearson’s Chi-squared test or Fisher’s exact test (categorical data).

Results: There were 325 patients who underwent RAL PEH repairs (265 primary, 60 recurrent) and were followed for a median (range) of 121 (5-2592) days. In the recurrent PEH group, patients had a median (range) of 1 (1-3) previous PEH operations. There were no differences in baseline demographics (age, body mass index, American Society of Anesthesiologists score, gender, insurance status, marital status, race/ethnicity, and pre-operative PPI use) between the groups. More patients in the recurrent PEH group had previous abdominal surgery (96.7% versus 68.3%, p<0.001), were more likely to have mesh placed (50% versus 34%, p=0.03), had longer operative times (170.4 versus 137.0 minutes, p=0.0006) and had longer hospital length of stay (66.2 hours versus 43.8 hours, p=0.001). Intra-operative complications, estimated blood loss, readmission and re-operation rates, recurrence, post-operative dysphagia and gas-bloat, and post-operative PPI use were not significantly different between the groups. There were no conversions or gastric/esophageal leaks in either group.

Conclusions: Although associated with longer operative times and hospital length of stay, RAL recurrent PEH repairs have similar perioperative and post-operative outcomes as compared to primary PEH repairs. Whether this is secondary to potential advantages afforded by the robotic platform deserves further study.
ABSTRACT

Geographic, Financial, and Social Burdens of Care in Families of Pediatric Cancer Patients

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Sponsored by: Mary Austin, M.D., M.P.H.
Supported by: The Department of Pediatric Surgery, McGovern Medical School at UTHealth
Key Words: Pediatric Cancer, Burden of Care

Health disparities in adults with cancer have been shown to significantly impact treatment outcome. However, health disparities are much less defined in the pediatric population. Additionally, financial, geographic, and racial disparities have each been independently correlated with increased burden of cancer treatment, but the impact of these burdens in families of children with cancer is poorly understood. Our objective is to develop and administer a cross-sectional survey to identify financial, social, and geographical barriers to care and describe their associated burden on parents and caregivers of children undergoing cancer treatment at M.D. Anderson Cancer Center (MDACC). The protocol for this study is currently undergoing IRB approval. The survey will be developed using a mixed methods approach, including the Impact on Family (IOF) scale and cancer-specific questions. The IOF scale is a survey instrument used to measure the impact of chronic childhood illnesses on families. Cancer-specific questions will be derived from semi-structured interviews conducted on 20 parents of children with cancer. Additionally, cognitive interviews will be conducted on another group of survey participants and exploratory factor analysis will be run. The survey items will be translated into Spanish, undergo linguistic validation, and administered to a final group of 200 participants. Finally, confirmatory factor analysis will be run to evaluate the validity of the cancer-specific questions. The selection of all participants will be non-random and purposeful to insure enrollment of a diverse study population reflective of the pediatric oncology patient population at MDACC. From their survey results, participants will each be given a comprehensive IOF score and dichotomized into a high impact or non-high impact group, revealing demographic characteristics associated with highly impacted families. The data acquired from this project will help identify the burdens that families of pediatric patients face when undergoing treatment, add to our understanding of health disparities in children and adolescents with cancer, and identify determinants of families at risk of significant burden to inform the development of supportive interventions.
ABSTRACT

Magnesium Sulfate Infusion During Fetal Meningomyelocele (fMMC) Repair to Reduce the Dose of Inhalational Anesthesia

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Sponsored by: Ranu Jain, MD, Department of Anesthesiology
Keywords: Inhalation anesthetics, sevoflurane, magnesium sulfate, myelomeningocele, spina bifida, in utero repair surgery, second trimester

BACKGROUND: Fetal myelomeningocele (fMMC) is a congenital defect in the vertebral column with herniation of the meninges and spinal cord in a sac-like protrusion. During the second trimester, this condition can be surgically treated through open fetal surgery, requiring profound uterine relaxation, fetal anesthesia, uterine tocolysis, and general anesthesia. However, animal model studies on general anesthesia using inhalational anesthetics have shown neurodevelopmental deficits and is not well studied in human fetuses. Sevoflurane, an inhalational anesthetic, is used in fMMC repair for both general anesthesia and uterine relaxation. Magnesium sulfate is a tocolytic that is administered during surgery to prevent contractions post-surgery. The objective of this study was to determine if starting magnesium sulfate (MgSO4) infusion at maternal skin incision during surgery, rather than at uterine closure, would reduce the requirement of inhalational anesthetic agents in fMMC repair.

METHODS: This is a prospective observational study of in-utero fMMC repair performed from September 2011 to August 2017. Comparison was performed between two groups: Group 1 - MgSO4 at uterine wall closure (September 2011 to January 2016), and Group 2 - MgSO4 at maternal skin incision (February 2016 to August 2017). 6 grams loading dose followed by 2 grams/hr of MgSO4 were given in all cases. The inhalational agent was titrated up until adequate uterine relaxation was attained, which was determined by the surgeon on palpation. Maternal demographics, anesthetic agents used during fetal surgery, intraoperative complications, and pregnancy outcomes were reviewed.

RESULTS: 53 patients were enrolled in the study; anesthesia records were available for 51 patients. There were 30 patients in Group 1 (uterine closure) and 21 patients in Group 2 (maternal skin incision). Average gestational age at surgery was 25.02 weeks (± 0.6). Average gestational age at delivery was 34.1 weeks (± 3.5). Both groups had 3 patients in which severe hypotension occurred that required treatment with ephedrine. Average MAC of sevoflurane was 1.53 (± 0.16) for Group 1 and 0.96 (± 0.22) for Group 2 with a p-value of <0.0001. Average phenylephrine rate and surgical time were not significantly different.

DISCUSSION: MgSO4 has been used for tocolysis to provide uterine relaxation following fetal repair. We found that early initiation of MgSO4 infusion at maternal skin incision was associated with lower inhalational anesthesia administration. There has been growing concern with the effects of high doses of these agents on long-term fetal neurodevelopmental outcomes. Using magnesium sulfate earlier may reduce the total exposure to the fetus.
ABSTRACT

Turner Syndrome: Karyotype and Severity of Associated Comorbidities

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Sponsored by: Siddharth Prakash, M.D., Ph.D, Dept. of Internal Medicine
Supported by: Siddharth Prakash, M.D., Ph.D, Dept. of Internal Medicine
Key Words: Turner Syndrome, Bicuspid Aortic Valve, Aortic Dilatation

TS is a common chromosomal disorder that affects approximately 1 in 2500 live female births. Complete or partial monosomy of one of the X chromosomes in a female is associated with various congenital heart defects (CHDs), which include aortic dilatation, coarctation of aorta, and BAV. Congenital cardiovascular defects related to BAV are the leading cause of death in TS women. The Turner Syndrome Network Registry (TRN Registry) and genetic sample repository can help address the lack of knowledge behind these CHDs by facilitating the recognition of demographic and genetic patterns in TS patients. This study compares frequency and severity of associated comorbidities between Turner Syndrome (TS) patients of mosaic (45,X/46,XX & others) and non-mosaic (45,X) karyotypes. TS patients were recruited into the TRN Registry, and gave blood and saliva samples after informed consent. Chromosomal microarrays were analyzed to confirm the genetic diagnosis and ascertain the karyotype. Demographic, socioeconomic, and medical history of our patients were abstracted from questionnaires and follow-up of medical records. ECGs, CT, MRI, and echocardiogram images were analyzed to determine the prevalence and severity of additional cardiovascular defects in the TS cohort. Since the establishment of the TRN Registry, 32 patients were identified and recruited. 26 patients had their karyotype confirmed: 13 had mosaic karyotype, and 13 had 45,X karyotype. Comparison of patients based on karyotype revealed there was not a statistically significant difference in the tested variables between mosaic and 45,X TS patients, confirmed by 2 tailed t tests with P > 0.05. Blood pressure measurements for 45,X and mosaic TS patients revealed: a) average systolic blood pressure was 116 mmHg and 118 mmHg, respectively (P = 0.142); b) average diastolic blood pressure was 76 mmHg and 77 mmHg, respectively (P = 0.224). Bloodwork for 45,X and mosaic TS patients revealed: a) average eGFR (corrected for gender and age via MDRD equation) was 163.45 mL/min/1.73m² and 120.39 mL/min/1.73m² respectively (P = 0.212); b) average HbA1C was 5.31 and 5.25, respectively (P = 1.0); c) average LDL was 87 and 98, respectively (P = 0.338). Fifteen ECG measurements for 45,X (8) and mosaic (7) TS patients revealed: a) average QTc interval was 437 msec and 453 msec, respectively (P = 0.381); b) average PR interval was 129 msec and 129 msec, respectively (P = 0.894); c) average QRS duration was 79 msec and 86 msec, respectively (P = 0.292). Data from the TRN registry revealed there was no statistically significant difference in blood pressure, ECG measurements, and lab values between 45,X and mosaic TS patients. Most members of the TS cohort were host to a wide array of CHDs, renal, reproductive, and chronic conditions. Among the more common complications were the CHDs (especially BAV). The higher frequency of these conditions predisposed TS patients to many cardiovascular complications, the most drastic being aortic aneurysms. Future research should stress the importance of patient education and active management of cardiovascular risk factors from an early age.
ABSTRACT
Using Client Language to Explore Mechanisms of Change in an Experimental Therapy for Comorbid Substance Use and Post-Traumatic Stress

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Sponsored by: Margaret Wardle, Ph.D., UTH Psychiatry Department
Supported by: The Saltzberg Fellowship Award
Key Words: Language, Therapy, PTSD, SUD

Background and Significance: Co-occurrence of post-traumatic stress disorder (PTSD) and substance use disorder (SUD) is associated with more severe SUD and lower success rates for SUD treatment. A novel treatment recently developed in our research group integrates cognitive processing therapy, an evidence-based treatment for PTSD, with standard cognitive behavioral therapy (CBT) for SUD in an attempt to improve treatment outcomes for comorbid SUD/PTSD. Developing more effective therapies requires identifying and refining the mechanisms at work during therapy as well as targeting therapies to individuals for whom that mechanism is relevant or effective. Although treatment outcome metrics are often standardized, few tools exist to analyze mechanisms active during therapy sessions. The Linguistic Inquiry and Word Count (LIWC) program measures use of speech categories, such as “negative emotion” and “past focus”, allowing objective quantification of language used in therapy, and thus objective indicators of topics and processes addressed in therapy sessions.

Hypothesis: With standard CBT for SUD as a comparator, we expected the novel therapy to evoke significantly higher levels of emotional engagement, as measured by the use of positive and negative emotion words. We also expected that patients’ distress tolerance, defined as the ability to weather adverse emotions, would correlate with emotional engagement in therapy and would prove particularly important to emotional engagement in the novel treatment. Finally, we explored the predictive capacity of language use for treatment outcomes.

Experimental Design: We analyzed language use during critical therapy sessions in a randomized, controlled trial in which patients with both PTSD symptomatology and SUD were assigned to either the novel integrated treatment or standard CBT for SUD alone. Transcripts of therapy sessions were analyzed by the LIWC and compared using (1) independent sample t-tests comparing emotion language across therapies and (2) moderated regressions examining the effects of distress tolerance on emotion language in each therapy. Finally, theoretically relevant LIWC categories were used as independent variables in exploratory regressions predicting treatment outcome scores.

Results: Unexpectedly, negative emotion language did not differ significantly between the two therapies. Instead, there was more use of positive emotion language in the standard therapy. Positive emotion language use in the standard therapy was further increased in patients with higher baseline distress tolerance. Finally, more use of positive language was associated with better PTSD, although not SUD, outcomes.
Conclusions: We concluded that positive emotional engagement, measured by positive emotion language, was actually higher in the standard therapy, that distress tolerance increased positive emotion in therapy, and that positive emotion correlated with observed treatment outcomes. Future research should explore methods of increasing distress tolerance to experimentally determine effects on both emotional engagement in therapy and treatment outcomes.
ABSTRACT

Student Attitudes and Perspectives on Social Determinants of Health in Preclinical Medical Education

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Class of 2020

Sponsored by: Rebecca B. Lunstroth, JD, MA, McGovern Center for Humanities and Ethics

Key Words: Social determinants of health, medical education, social disparities

It is becoming increasingly apparent that in addition to being knowledgeable in basic sciences and clinical skills, medical students are also required to be knowledgeable in the social contexts that influence the course of disease. In order to best educate the future leaders of healthcare, we wanted to learn more about our student body. The purpose of this study was to determine if there is a correlation between student demographics and their attitudes on social determinants of health in the medical school curriculum. A voluntary and anonymous survey was distributed through email to the student body of McGovern Medical School and assessed student confidence and attitudes about working with patients affected by social determinants of health and learning about the subject matter in the current curriculum. Responses were recorded on a five-point Likert scale. Out of 89 participants in the survey, our results showed a significant portion of students who were first generation college graduates were more confident in working effectively with disadvantaged populations as well as students who had previously worked with a community-based organization. We found that other demographics, such as gender, race, and religion, showed no significant correlation on student attitudes towards social determinants of health. With this information we plan to create more educational experiences that expose students to social determinants of health in multiple educational modalities in order to increase student confidence prior to clinical clerkships.
ABSTRACT

Can we trust the clinic diagnosis of hypertension in pediatric patients with respect to White Coat Syndrome?

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Sponsored by: Joshua Samuels, MD, MPH
Supported by: NIH/NIDDK
Key Words: White coat hypertension, masked hypertension, hypertension, pediatrics

Along with the recent obesity epidemic in the United States, we have seen the pediatric distribution of blood pressure (BP) level shift towards higher values. This elevated BP in children has been shown to be associated with increased incidence of early markers of atherosclerosis such as left ventricular hypertrophy. Making an accurate diagnosis could subsequently lead to better and more efficient care with respect to hypertension. We followed up on a previous 2001 study titled Evaluation of white coat hypertension in children to determine any increase or decrease in the prevalence of white coat hypertension seen at the UTHealth pediatric hypertension outpatient clinics.

A retrospective chart review was conducted of 219 pediatric hypertension patients born after 1995 assessed by 24-hour ambulatory blood pressure monitoring (ABPM) at the UTHealth pediatric hypertension clinics from January 1st, 2015-December 31st, 2016. Our study found white coat hypertension to be present in only 13% of our subject pool. Masked hypertension was found in 12% of the population. The overall concordance rate of clinical and ambulatory BP (not white coat, masked, or missing American Heart Association (AHA) classification) was 63%. After controlling for all other covariates, concordance was associated with higher clinical systolic blood pressure (SBP) or diastolic blood pressure (DBP) and younger age.

Past research suggests varied prevalence regarding white coat hypertension (0.6-88%) and a more narrow range of reported masked hypertension (7.6-15%). Our study suggests that the rate of white coat hypertension seen in our local population is markedly less than most reported statistics found in the literature. However, we saw a 12% prevalence of masked hypertension which is in line with previous estimates. Although hypertension has been widely studied in adults, there are fewer published studies employing ABPM in the pediatric population. With these results, more accurate evaluation and treatment of hypertension can be administered in children.
ABSTRACT

Obesity Association with Breast Cancer Related Lymphedema

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Sponsored by: NIH R01 CA201487, NIDDK 2 T35 DK007676-22
Supported by: Melissa Aldrich, PhD, Eva Sevick, PhD, UTHealth Center for Molecular Imaging
Key Words: Breast cancer related lymphedema, obesity, inflammation, chemotherapy

Breast cancer-related lymphedema (BCRL) is a progressive disease encountered by up to 40% of breast cancer survivors, currently numbering more than three million women in the United States (1.2 million with BCRL). BCRL is characterized by swollen arms and trunks, frequent cellulitis attacks, pain, and depression. BCRL can appear at any time after cancer treatment, even years later. BCRL occurs more frequently in patients receiving axillary lymph node dissection (ALND) and radiation treatment, but the etiology is unknown. A potential risk factor for BCRL may be obesity. The relationship between fat cell growth and lymph stasis is well known—stagnant lymph provides molecular factors to adipose cells that encourage growth and multiplication. In this project, the relationship between ghrelin, leptin, and adiponectin (markers of obesity) to lymphatic pulsing was explored.

Blood samples were taken and plasma levels for ghrelin and leptin were measured using commercial ELISA kits. Although the sample size was 10 subjects, we expect to see trends that will be reflected in the larger, full-study sample size of 100 study subjects. Lymphatic pulsing was recorded using NIRFLI technology and was loaded into ImageJ software (NIH) for analysis. Images were evaluated for lymphovascular anomalies and lymphatic pulsing frequencies (pulses per minute).

After analyzing the pulsing and ELISA data for leptin, ghrelin, and adiponectin, slight trends were observed. It’s expected these trends would be stronger if the full study of 100 subjects was analyzed. Before conducting the experiment, it was expected that impaired lymphatic function (decreased pumping) would be correlated with obesity markers, like higher leptin and lower adiponectin and ghrelin. The results showed that 7/10 patients had marked decreased lymphatic pumping in their affected arm than the normal arm, which goes to show that breast cancer surgery can impair lymphatic function. Overall, adiponectin decreased with higher pulsing, which was unexpected. We hypothesized that higher adiponectin would correlate with higher pulsing, because typically, the higher these values are, the healthier the subject is. Leptin increased with higher pulsing, which was also unexpected, as we would expect leptin values to decrease with higher pulsing. Ghrelin values did not have an obvious trendline. Although the results were not anticipated, observing specific trends will better help us identify possible risk factors for developing BCRL in the future.
ABSTRACT

Functional Engraftment of Airway Basal Stem Cells for Future Cystic Fibrosis Therapy

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Sponsored by:  
Dr. Brian R. Davis

Supported by:  
Dr. Brian R. Davis, and the McGovern Medical School Dean’s Office

Key Words:  
Cystic Fibrosis, Basal Cells, Mouse Model

Cystic fibrosis is an autosomal recessive genetic disease that affects 1 out of 3000 individuals. Mutations in the CFTR gene causes the transcription and translation of a non-functional chloride channel that is necessary to mediate fluid flow by creating an osmotic gradient. CFTR-mediated fluid flow is critical to the production of sweat, pancreatic enzymes, and mucus, and the loss of CFTR functionality leads to pathology of CF. Although CF affects a variety of organs (e.g. lung, pancreas, and intestine), it is the loss of lung mucociliary clearance that is the primary driver of morbidity and mortality. Gene editing technologies have made it possible to correct the CFTR gene in vitro but delivering the corrected protein to living individuals remains an area of investigation. Basal cells are a stable population of stem cells that reside in the respiratory epithelium of the lung, and are able of giving rise to all the cell lineages that normally make up the epithelial layer. Thus, delivery of CFTR corrected basal cells could act as an efficient vehicle to provide functional CFTR to cystic fibrosis patients.

In an effort to establish an airway basal cell engraftment model we first established a model of mouse airway injury. Mice were treated with naphthalene IP at 160-380 mg/kg body weight. Two days post treatment, lungs were collected and immunostained for basal and secretory cell markers (K5 and CCSP, respectively). Naphthalene injury led to a reduction in basal cell numbers in the trachea where they reside, and a total denuding of secretory cells from the conducting portions of the lungs. The murine lung K5+ basal cells showed healing at days 2, 4, and 14 post treatment, with basal cells reconstituting in the trachea first, then moving into the mainstem bronchi. By day 14, the K5+ basal cell distribution and intensity was similar to untreated samples. CCSP+ secretory cells did not recover even by day 14.

Human airway basal cells were labelled then delivered to naphthalene-injured mice. We expanded human airway basal cells in dual-SMAD inhibition media (Mou et al, 2016), then labeled the basal cells with GFP-lentivirus. These cells were then FACS sorted to enrich for the GFP+ population. GFP+ labelled human basal cells were delivered to mice 2 days post treatment with 275 mg/kg naphthalene body weight. Mice were euthanized and lungs collected at day 2. Sections were first analyzed for GFP, then stained for Laminin A&C (human nuclear envelope proteins) to assay for cell engraftment. Preliminary results gives evidence for some presence of human cells in the injured mouse airway.

Here we have developed a system to culture, manipulate, and label human airway basal cells for transplant. We have also laid the groundwork for introduction into a mouse model by
showing damage to the mouse respiratory epithelium in response to naphthalene treatment. In the future, this system and methods could be used for gene therapy and live modeling of airway diseases, Cystic Fibrosis for example, which is amendable to genetic editing.
ABSTRACT
Development of a New Cellular Model of Cluster Headache: Primary Mouse Trigeminal Ganglia Cultures as a Treatment Model

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Sponsored by: Mark J. Burish, M.D., Ph.D., Vivian L. Smith Department of Neurosurgery
Supported by: Mark J. Burish, M.D., Ph.D., Vivian L. Smith Department of Neurosurgery; The University of Texas Health Science Center at Houston McGovern Medical School – Office of the Dean
Key Words: Cluster headaches, circadian, trigeminal ganglia

Background: Cluster headaches commonly demonstrate a clock-wise regularity in symptom onset, with 82% of patients having headaches at the same time of the day and 12% at the same time each year. This suggests an association between cluster headaches and potential circadian abnormalities. Furthermore, there has been evidence that some of the more effective therapeutic treatments for cluster headache prevention may modulate the circadian cycle, for example expression levels of the Period2 gene. Unfortunately, current treatments are ineffective for many patients. Thus, the development of neuronal models is important to explore the effects of other treatments on circadian expression, with the ultimate goal of identifying new treatments for cluster headache.

Methods: Trigeminal ganglia were harvested from transgenic mice expressing Period2::Luciferase, in which the amount of light released can be used as a marker of Period2 gene expression. The ganglia underwent enzymatic digestion in a papain solution followed by a dispase and collagenase IV solution. The digested ganglia were subsequently passed through a 100 uM filter to remove undigested debris. The isolated neurons were then plated with F-12 culturing media onto 35 mm dishes, treated in advance with poly-d-lysine and laminin to promote adherence. The neuronal cultures were incubated at 37° C and media was changed at 24 hours following initial seeding to remove residual debris. Neuronal cultures confluent at 72 hours following initial seeding were treated with dexamethasone for 1 hour to synchronize the circadian rhythms. Following synchronization, the culture media was replaced with recording media containing luciferin and placed into a lumicycle. The real-time luminescence of each neuronal culture was recorded over a 72-hour period or after 3 periods of oscillation. The cultures were then treated with either 3 uM or 10 uM verapamil and placed back into the lumicycle to observe any associated circadian effects.

Results: The trigeminal ganglia dissociation showed promising results, as the initial seeding produced confluent cultures. These cultures also displayed an observable oscillatory pattern in the lumicycle after synchronization and application of recording media. Interestingly, treatment with 3 uM and 10 uM verapamil (a cluster headache preventive medication) appeared to decrease and increase the amplitude of oscillation, respectively. However, due to low sample size, no significant deviation could be calculated.
Conclusion: Primary mouse trigeminal ganglia cultures are a promising field for examining the effects of cluster headache treatments on circadian rhythms. Despite a lack of sample size necessary for significance, circadian rhythms and associated modulation were observable.
ABSTRACT

Identification of Quorum Signaling Response Elements in *C. difficile* strain 630

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Sponsored by:  Charles Darkoh, PhD, UTHSC School of Public Health, Center for Infectious Disease

Supported by:  Charles Darkoh, PhD, UTHSC School of Public Health, Department of Epidemiology, Human Genetics and Environmental Sciences, Center for Infectious Disease; Office of the Dean

Key Words:  *C. difficile* 630, quorum signaling, Agr, TI signal

**Background:** *Clostridium difficile* is one of the most commonly acquired nosocomial infections in the United States, with its incidence increasing over the last several decades. This enteropathogen causes disease by producing toxins A and B. These toxins have become promising targets for therapy due to the propensity of *C. difficile* to develop antimicrobial resistance. Toxin synthesis is regulated by an accessory gene regulator (Agr) quorum sensing system, which is mediated by a thiolactone signal (designated as TI). There are two physically separated Agr systems within the *C. difficile* genome, which are designated Agr1 and Agr2. Agr1 is present in all sequenced strains and only encodes genes required for TI signaling. However, Agr2 is present in hypervirulent strains and contains genes required for both TI signal synthesis and response, which is necessary for toxin production activation. Surprisingly, *C. difficile* strain 630 encodes only the Agr1 locus and lacks Agr2, but is still able to synthesize toxin. This suggests that 630 utilizes unidentified non-Agr designated genes to sense and respond to the TI signal. We hypothesized that 630 utilizes a two-component system, comprised of a histidine kinase and a response regulator, to respond to the TI signal. We anticipate that this two-component system may be transcriptionally regulated by the TI signal.

**Methods:** *C. difficile* strain 630 was incubated both with and without TI signal for 4 hours, and a toxin assay was performed to confirm that only the 630 exposed to TI signal produced toxin. RNA was extracted and subsequently used to synthesize cDNA. Quantitative real-time PCR was performed using the cDNA to assess expression levels of 42 pairs of two-component systems present in the genome of the 630 strain. Quantification cycles (Cq) were compared to determine relative expression of target genes in TI-incubated 630 compared to 630 not exposed to TI.

**Results:** No single gene target showed significant overexpression based on Cq values in cDNA synthesized from cells exposed to the TI signal compared to the unexposed cells.

**Conclusions:** Our results to date are inconclusive, as no single two-component system seemed to have significantly increased expression in cells exposed to the TI signal. We plan to repeat the experiment using cDNA synthesized from an Agr1 mutant exposed to the TI signal with the expectation that this causes significant overexpression of the cognate two-component system.
ABSTRACT

Walking Impairment Questionnaire Association to Subclinical Peripheral Artery Disease in the Cameron County Hispanic Cohort

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Sponsored by: Susan P. Fisher-Hoch, MD  
Supported by: NIH/NIDDK: 5 T35 DK 7676-24; Bruce C. Kone, MD  
Key Words: Peripheral artery disease, ABI, TBI, walking impairment questionnaire.

Background: Prevalence and associations for Peripheral Artery Disease (PAD) in Mexican Americans (MA) have not been well characterized. The aim of this study was to find functional ability differences between those who have PAD and those who do not using the Walking Impairment Questionnaire in a random population sample of MA adults in Cameron County, Tx.

Methods: Subjects underwent measurement of bilateral ankle and toe brachial indices (ABI, TBI) using a Doppler system in order to identify those with PAD (ABIs 0.9, TBIs 0.7). The higher and lower of the two pedal pressures for each limb were used for calculating ABI-High (Traditional method) and ABI-Low (Sensitive Method), respectively. In addition, toe pressures were used for calculating TBI. The Walking Impairment Questionnaire assesses leg pain symptoms, walking speed, and walking distance. A subject receives a score out of a hundred after each section to describe their function percentage (a lower score points to increased impairment). Questionnaire scores were compared between people that had PAD and those that did not.

Results: Of the 326 participants, 9 subjects were classified as having PAD using the ABI-High definition, 32 subjects had PAD using the ABI-Low definition, and 54 subjects had an Abnormal TBI. Individuals classified as having PAD in the ABI-High and ABI-Low categories did not show a significant difference in the Walking Pain Symptoms score when compared to normal. Nevertheless, subjects with PAD in the ABI-High and ABI-Low categories had significantly lower Walking Speed and Distance scores when compared to normal.

Conclusions: The Walking Impairment Questionnaire could serve as an accessible and affordable tool for early screening of the disease in individuals with subclinical PAD and underlying decreased leg functions. This could lead to a decrease in disease progression by implementing timely risk factor modifications and early interventions or treatments.
ABSTRACT

Modulation of the function of eIF4F complex by eIF4A inhibition in Merkel cell carcinoma cells: regulation of oncogenes and a new therapeutic implication

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Sponsored by: Stephen K. Tyring, MD, PhD, MBA, Department of Dermatology, McGovern Medical School at Houston
Supported by: Stephen K. Tyring, MD, PhD, MBA, Department of Dermatology and the Office of the Dean, McGovern Medical School at Houston

Key Words: Merkel cell carcinoma, Silvestrol, Survivin, Mcl-1

Background: Merkel cell carcinoma (MCC) is an aggressive neuroendocrine skin cancer with rising incidence in immunocompromised patients. The recently discovered Merkel cell polyomavirus (MCPyV) is clonally integrated in over 80% of MCC tumors, and the carcinogenic mechanism of MCPyV is dependent upon activation of mTOR and 4E-BP1 pathways. The former pathways drive carcinogenesis through recruitment of eukaryotic initiation factors (eIFs) and assembly of the eIF4F complex, composed of eIF4A, eIF4E, and eIF4G at the 5'-m7G cap. The direct eIF4A inhibitor silvestrol, previously characterized in other cancer cells, has been found to promote cell cycle arrest, translation inhibition, and autophagy. Such studies noted reduced levels of cyclins B1 and D1, Bcl-2, c-myc, survivin, and Mcl-1; however, if silvestrol has similar implications in the treatment of MCC cells requires further investigation.

Methods: MCC cell lines derived from MCPyV-positive MCC tumors (MS-1 and MKL-1) and MCPyV-negative MCCs (MCC13) were cultured and treated with silvestrol for 24 and 48 hours. Protein lysates were extracted and subjected to SDS-PAGE and Western blot analysis. Antibodies against Mcl-1 and survivin were applied.

Results: We utilized the MCC cell lines, MS-1 and MKL-1 (derived from MCPyV-positive MCC tumors), to analyze the impact of silvestrol on eIF4A. Our data showed that treatment of MS-1 and MKL-1 cells with the direct eIF4A inhibitor silvestrol resulted in marked decreases in downstream oncoprotein expression. Specifically, our data demonstrated that eIF4F complex inhibition resulted in downregulation of survivin and Mcl-1 in both 24- and 48-hour treatment groups. Next, we used an MCPyV-negative MCC cell line (MCC13) to further characterize the impact of eIF4F complex inhibition via silvestrol treatment. Specifically of interest was survivin modulation in the MCC13 cell line, as previous studies have suggested that the oncogene is activated by MCPyV. Interestingly, we found that survivin was markedly downregulated in 24- and 48-hour treatment groups in the MCC13 cell line, too.

Conclusions: Overall, our findings demonstrate that silvestrol's action in blocking eIF4A results in the downregulation of important oncogenes like survivin and Mcl-1 downstream of the eIF4F complex. As the eIF4F complex governs the downstream mechanisms of the mTOR/4E-BP1 axis, crucial for Merkel cell carcinogenesis, our findings may suggest an intriguing novel possibility of utilizing eIF4A inhibitors for treatment of MCCs. Future work
should include adjusting silvestrol doses based on IC50 data and carrying out protein profiling assays to better characterize the effect of the treatment on the three cell lines.
ABSTRACT

The Role of IL-6, MCP-1, TLR4 Signal Pathway and MAPK Signal Pathway in Paclitaxel Induced Peripheral Neuropathy

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Sponsored by:  Patrick M. Dougherty, PhD, Professor, M.D. Anderson Cancer Center  
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Supported by:  NCI R01 CA200263 and the H.E.B. Professorship in Cancer Research

Key Words:  CIPN, Paclitaxel, DRG, Cytokines

Paclitaxel is the front-line chemotherapeutic agent used to treat the most common solid tumor cancers, including those of the lung, breast and ovary. Paclitaxel interferes with the growth and division of cancer cells by promoting the assembly of stable but dysfunctional microtubules. Chemotherapy Induced Peripheral Neuropathy (CIPN) is a debilitating and persistent dose-limiting side effect of Paclitaxel treatment. The mechanisms underlying CIPN are extremely complex, therefore comprehensive and cohesive process behind it have yet to be fully elucidated. In vivo studies have provided explanations for many of the processes surrounding CIPN. The aim of this study was to provide further evidence for the mechanisms underlying Paclitaxel induced CIPN by using an in vitro model of Paclitaxel treatment. Cytokines have been identified as key participants in the pathophysiology driving CIPN. The focus of this research is targeted on IL-6 and MCP-1, the TLR4 signal pathway, and the MAPK signal pathway. By providing evidence for their role in an in vitro paclitaxel treated primary rat DRG culture model, we hope to gain a better understanding of the mechanisms behind paclitaxel induced CIPN as well as provide a platform from which potential therapeutics and further research may be based on. In primary rat DRG culture incubated with Paclitaxel, TLR4 and MyD88 were upregulated at 48h, and the immediate down-stream signal molecules Mitogen-activated protein kinases (MAPK), Extracellular signal related kinase (ERK1/2) and p38 but not c-Jun N terminal kinase (JNK), were upregulated at 2h and 48h after paclitaxel incubation using western blot. This upregulation could be prevented by pretreated with TLR4 antagonist (LPS-RS). IL-6 and MCP-1 were released into culture medium detected by using ELISA and upregulated in cultured cells using western blot after paclitaxel treatment. IL-6 and MCP-1 staining was co-localized to TLR4-positive cells using Immunohistochemistry. Whole-cell patch clamp recordings in rat DRG neurons revealed that MCP-1 induced spontaneous action potentials and enhanced the amplitude of membrane potential oscillation. These results implicate that IL-6, MCP-1, TLR4 signaling pathway and MAPK signaling pathway may be important in the induction and maintenance of paclitaxel related CIPN.
ABSTRACT

Tunneled Central Venous Catheters in Pediatric Intestinal Failure Patients: A Single Center Review

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Sponsored by: Dr. Kuojen Tsao, MD, Pediatric Surgery
Supported by: Dr. Kuojen Tsao
Key Words: Complications/Contributors to Broviac Complications

Introduction: Children with intestinal failure (IF) often require a tunneled central venous catheter (CVC) for parenteral nutrition. The purpose of this study was to characterize complications after CVC placement and contributors to line loss in IF pediatric patients.

Methods: A retrospective chart review of pediatric (<18 years) IF patients who had a silicone tunneled CVC newly inserted or exchanged over a wire from 2012-2016 was conducted. Patient demographics, catheter insertion service (surgery vs. interventional radiology), procedure type (new vs. exchange), vessel and complications related to CVCs were evaluated. Complications included dislodgement, infection, break or mechanical malfunction, and occlusion. An ethanol lock protocol for silicone CVCs in IF patients was instituted in January 2012. Descriptive statistics, t-test, ANOVA, chi², and linear regression were used for analysis.

Results: 29 IF patients with tunneled CVCs were identified with 191 lines and 17,598 line days. Patients had a median age of 19.7 months (IQR 8.7 – 40.8) at the time of line insertion and had a median of 5 catheters (IQR 2-9). Necrotizing enterocolitis was the most common etiology of IF (59%). There were 13.4 complication events per 1000 line days. Line breaks were the most common complication (4.7 events/1000 line days) followed by occlusion (3.4 events/1000 line days), infection (3.0 events/1000 line days) and dislodgement (2.2 events/1000 line days). Median life of catheters was 54 days (IQR 24-140). Line lifetime did not vary by insertion service (p=0.33), vessel (p=0.82), or procedure type (new vs. exchanged, p=0.08). Younger age was associated with shorter line life (p=0.04). Reason for line removal included dislodgement (21%), infection (23%), occlusion (21%), line breaks/malfunction (31%), and other reasons (5%). On multinomial regression adjusting for age and procedure type (new vs. exchanged), dislodgement was associated with newly placed lines (RR 6.9, 95% CI 2.2-21.7). Dislodgement was the cause for removal in 45% of new lines but 11.5% of exchanged lines. Accounting for procedure type and cause of removal, age was not independently associated with catheter life (p=0.16).

Conclusion: Pediatric IF patients depend on tunneled central venous catheters which have frequent complications. In this cohort, dislodgement of catheter was an unexpectedly common contributor to complications and loss of access, particularly in newly placed lines.
Opportunities for simple interventions, such as closer attention to securing sutures and dressing application, should be investigated to mitigate these preventable complications.
ABSTRACT

Isolating Mammalian Plasma Membranes by Physical Disruption of Cells

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Sponsored by: Levental Lab, NIH NIDDK
Keywords: Plasma membrane model, plasma membrane isolation, lipidomics, lipid rafts, Giant Plasma Membrane Vesicle, GPMV, MDCK, HEK, Madin-Darby Canine Kidney, Human Embryonic Kidney 293T, plasma membrane patch.

Lipid rafts are organizing platforms within biological membranes that have been implicated in many physiological processes, including cell signaling and intracellular trafficking. Models of cellular plasma membrane (PM) are used to understand lipid rafts by studying membrane biophysical properties, like liquid-liquid phase separation. Giant plasma membrane vesicles (GPMVs) are isolated cellular PMs that maintain the native lipid and protein composition of the PM, in contrast to previously used synthetic models that contain only a limited set of components. GPMVs are made by chemically shocking mammalian cells, resulting in the loss of membrane asymmetry and an assembled cytoskeleton, two features that may be important in determining the physiological state of the plasma membrane and its organization (i.e. lipid rafts). With these caveats in mind, the objective of our project was to develop a PM model that more closely resembles the native physiological state of living cell membranes. We hypothesized that if physical, rather than chemical, disruption is used to isolate patches of cellular PMs, a model retaining native asymmetry and assembled cytoskeleton would result. Initially, we attempted cell disruption via hypo-osmotic shock, by applying water to adherent cells. The results from this procedure were unreliable and unreproducible, often resulting in large contaminations of intact whole cells along with areas of isolated PM patches. Instead, more consistent results (>90% by area cell-free PM patches) were found by freezing Madin-Darby Canine Kidney (MDCK) or Human Embryonic Kidney 293T (HEK) cells in water, thawing, and washing away cellular contents not attached to the plate. Immunofluorescence showed successful removal of nuclei and lysosomes, although some residual endoplasmic reticulum (ER) and golgi apparatus membrane remained. Western blotting was performed to quantify the purity of the preparations. An increase in the PM marker protein relative to total protein was observed, but an increase in ER marker protein was also observed. Future work will include using the patches for microscopic characterization of membrane physical behaviors, and optimization of patch production for PM isolation and lipidomics.
ABSTRACT

Degree of Cirrhosis Influences Survival Following Transarterial Chemoembolization for the Treatment of Unresectable Hepatocellular Carcinoma

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Sponsored by:  Dr. Curtis J. Wray, MD, General Surgery, Surgical Oncology
Supported by:  Dr. Curtis J. Wray, MD
Key Words:  Hepatocellular carcinoma, transarterial chemoembolization, cirrhosis

Background: Data regarding transarterial chemoembolization (TACE) as a treatment for unresectable hepatocellular carcinoma (HCC) in the context of extensive cirrhosis is ambiguous. Following TACE, 10-20% of patients studied experienced hepatic decompensation. As of now, little evidence delineates circumstances in which TACE would be an unsuitable therapeutic modality.

Objective: Our experiment analyzes whether TACE operation within our institution has greater beneficial outcomes compared to best supportive care (BSC) or systemic therapy for unresectable HCC with cirrhosis.

Methods: Data of institutional HCC cases treated with TACE (Doxorubicin eluting beads), chemotherapy, or BSC was compiled including standard demographic variables. Patients treated with surgery or ablation were excluded from this study. Post-2008, the data contained a multidisciplinary tumor board (surgical oncology and interventional radiology) coded as a binary variable. Using age, stage, gender, alpha-fetoproteins, albumin, MELD score at diagnosis and time period, inverse probability of treatment weighted propensity scores were created. These scores were included in a Cox proportional hazards model to estimate survival. In addition, variables associated with survival less than 90 days (S<90D) were identified via a logistic regression model.

Results: 746 HCC patients were included in this study. Treatment included: TACE only 141 patients (19%), chemotherapy only 135 (18%), BSC 415 (56%) and both 55 (7%). The percentage of patients receiving TACE tripled (12% to 33%, p<.05) after utilization of the tumor board in 2008. TACE increased mean survival an additional 9.9 months (95%CI:0.82-18.9,p<0.05) from an estimated mean survival of 12.0 months (95%CI:9.83-14.2, p<0.05) of patients treated with either chemotherapy or BSC. For patients treated with TACE, variables associated with S<90D included MELD (OR 1.16, 95%CI:1.04-1.29, p<0.01) and stage III (OR 12.1, 95%CI:1.40-16.3, p<0.03). Stage I&II patients receiving TACE had a greater than 50% probability of survival more than 90 days if they also had a MELD score of less than 22. Stage III HCC patients receiving TACE only had a similar survival benefit if their MELD score was less than 15.
Conclusions: Compared to chemotherapy or BSC, locoregional TACE significantly improved survival in HCC patients with cirrhosis. With increasing MELD scores, especially above 15, benefit of TACE diminishes for unresectable HCC.
ABSTRACT

The Oncometabolite D-2-Hydroxylutarate Activates Autophagy in Myocytes

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Sponsored by: Heinrich Taegtmeyer, MD, DPhil Department of Internal Medicine
Supported by: Heinrich Taegtmeyer, MD, Department of Internal Medicine, The University of Texas at Houston Medical School – Office of the Dean
Key Words: D2-HG, metabolism, oncometabolite, autophagy, LC3, AMPK, mTOR

Background: About 20% of acute myeloid leukemias (AMLs) harbor mutations of isocitrate dehydrogenase (IDH) 1 and 2, which reduce α-ketoglutarate (α-KG) to the oncometabolite D-2-hydroxylutarate (D2-HG). Elevated serum D2-HG levels in AML are accompanied by systemic effects including heart failure. It was recently shown that D2-HG impairs cardiac contractility by inhibiting the Krebs cycle enzyme α-Ketoglutarate dehydrogenase (α-KGDH), and causes heart as well as skeletal muscle atrophy. Therefore I am now proposing that D2-HG activates autophagy in myocytes.

Methods: I used L6 myocytes (L6Ms, rat skeletal muscle cell line) as a model. Cells were grown to confluency and differentiated to myotubes using DMEM containing 1% penicillin/streptomycin and 5% Fetal bovine serum (FBS). Cells were treated in FBS-free culture medium for 24 h with or without D2-HG (1 mM). To assess autophagic flux, cells were cultured under the same conditions in presence of 0.1 μM Bafilomycin A1 (BafA1) and subjected to immunoblotting. Nucleoporin 62 (p62) shuttles ubiquininated proteins to the autophagosome, thereby facilitating the clearance of ubiquitinated proteins. I determined the protein expression of p62 at 2, 4, and 6 hours in response to D2-HG. I further measured gene expression of the muscle-specific ubiquitin E3-ligases atrophy gene-1/muscle atrophy F-box (Atrogin-1/MAFbx) and muscle ring-finger protein 1 (MuRF1) and genes encoding for proteins regulating autophagy (e.g. Beclin1, p62) using qRT-PCR.

Results: D2-HG increased the conjugation of microtubule-associated protein 1A/1B-light chain 3 to phosphatidylethanolamine (LC3-II) in differentiated L6 myocytes within 24 h, which is consistent with increased recruitment of LC3 to autophagosomal membranes. In presence of the lysosomal inhibitor BafA1, D2-HG-treated cells showed increased expression of LC3-II, which is consistent with increased autophagic flux. I further observed increased phosphorylation and activation of AMPK, while mTOR and Akt phosphorylation was decreased. D2-HG reduces the intracellular ATP/AMP ratio which in turn activates AMPK and inhibits mTORC1, resulting in stimulation of autophagy and inhibition of protein synthesis by intersecting pathways. At the same time, I observed that the expression of p62 decreased 4 h after addition of D2-HG and returned back to control levels after 6 h. Binding of the autophagosome to the lysosome causes degradation of p62 as observed in my experiments. Gene expression of Atrogin-1/MAFbx and MuRF1 was unchanged, while BECN1 (Beclin1) as well as LC3 started increasing 6 h after addition of D2-HG and stayed significantly elevated.
after 16 h. My data indicates that addition of D2-HG increases the gene expression of proteins regulating autophagy.

**Conclusion:** D2-HG promotes autophagy activation through post-translational and transcriptional mechanisms.
Inter- and Intra-observer Variability in Assessment of Femoral Head Alpha-Angle: A Comparison Between CT and MRI 3D Modeling

RAMZY MEREMIWKU  McGovern Medical School at UTHealth  Class of 2020

Sponsored by:  Nicholas Beckmann, MD, Department of Diagnostic Imaging, Derek West, MD, Department of Interventional Radiology

Supported by:  Summer Research Project; Nicholas Beckmann, MD, Derek West, MD

Key Words:  Femoral Head, Alpha Angle, Inter-Intra Observer, 3D MRI, 3D CT

Femoroacetabular impingement (FAI) is a common cause of anterior hip pain. FAI can be caused by over-coverage by the acetabulum (pincer-type FAI) or by abnormal morphology of the anterosuperior femoral head (CAM-type FAI). In young adult and pediatric patients, the CAM-type of FAI predominates. When the CAM-deformity of the femoral head is severe, resection of a portion of the femoral head may be required to relieve the impingement. Accurate assessment of the CAM-deformity on preoperative imaging can be useful for planning. Preoperative assessment of CAM-deformities involves subjective assessment by the surgeon as well as objective assessment by measuring the alpha-angle. The alpha angle” is an angular measurement that helps quantify the severity of the CAM-deformity. Larger CAM-deformities are associated with larger alpha-angles.

3D CT has been the gold standard for preoperative assessment of CAM-deformities due to its superior depiction of the deformity compared with 2D CT and radiography. More recently, studies have been performed to demonstrate 2D MRI capability to diagnosis CAM-deformities. Utilization of MRI is preferred to CT because MRI spares patients from exposure to ionizing radiation. In addition, MRI has the ability to characterize labral tears and chondromalacia, two pathologies commonly associated with CAM-deformities that influence surgical management. However, MRI has not historically been capable of performing 3D modelling of the bone. Depending on plane of imaging, MRI of CAM-deformities suffers the same limitation of variability in alpha angle that is seen in 2D CT imaging. To date, there have been few studies using 3D MRI modelling of the femoral head to assess CAM-deformities, and there is no commercially available software to perform 3D MRI modelling.

This study aims to demonstrate that the interobserver variability of alpha-angle measurement using 3D MRI modelling is comparable to 3D CT modelling. We believe the images are comparable. The observers will be a rising 2nd year medical student and accredited board-certified musculoskeletal Radiologist. Results showed that the alpha-angle degree differences between 3D CT and 3D MRI were not clinically significant with a 95% confidence interval. Compared to 3D CT modeling, MRI exhibited statistically significant resolution and bone modeling, with a P value < 0.05. An interobserver correlation coefficient (ICC) was calculated to determine the amount of agreement between the two observers. ICC values were designated as Poor-Fair-Good-Excellent with 80% of ICC values rating as Fair (Fair = ICC from 0.4 - 0.59). 3D CT is the gold standard for FAI-CAM, but 3D MRIs can offer a great alternative when patients
may also suffer from radiation sensitivity, associated labial tears, or chondromalacia along with their FAI-CAM diagnosis.
ABSTRACT

Pain Management Following Primary Palatoplasty:
Improving Transition of Care

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Sponsored by: Matthew R. Greives, MD, Department of Pediatric Surgery
Key Words: Pain Management Following Palatoplasty

Background: Post-operative pain following palatoplasty may cause feeding and swallowing difficulty. Dedicated pediatric pain service teams provide consistent, controlled pain management during the inpatient phase of recovery. Proper pain management following transition from inpatient stay to outpatient status is important to prevent readmission and emergency department visits for pain. Our study focused on improving outpatient pain management and patient satisfaction by improving transition protocols for patients following primary palatoplasty.

Methods: An IRB approved retrospective analysis was performed for 56 patients undergoing primary palatoplasty. Data was obtained for length of stay, pain scale scores, inpatient narcotic dosages, and inpatient readmissions/emergency department visits. Separately, an IRB approved prospective trial of 27 patients who underwent primary palatoplasty was also performed. Patients were identified and consented during their preoperative clinic visit. Following surgery, patients were assessed for the same metrics as the retrospective cohort. Prior to discharge, parents were required to fill narcotic prescriptions. The pediatric pain service team focused on teaching parents improved pain management strategies like augmenting narcotic medications with non-narcotic medications. Parents also received a narcotic usage chart to record the outpatient narcotic dosages per day. Parents reported results to the surgeon during a two-week follow-up visit and participated in a five-point satisfaction survey (1=very unsatisfied, 5=very satisfied).

Results: Data was obtained retrospectively for 56 patients and prospectively for 27 patients who underwent primary palatoplasty. No significant difference was observed for length of stay, pain scale scores, or inpatient narcotic dosages per day. These results demonstrate consistent inpatient pain management between the cohorts. Outpatient medication logs were completed for 9 (33%) patients showing a continued decrease in narcotic usage at home with no spike post discharge day 1. Patient satisfaction surveys were completed by 12 (44%) parents and showed high satisfaction levels for inpatient pain management (4.66 ± 0.49) and even higher satisfaction levels for comprehension (5.0 ± 0) and management of pain (4.92 ± 0.29) at home. Inpatient readmission/emergency department visits for palatoplasty decreased from 10.7% (6) following the previous protocol to 0% with the new transition protocol (p=0.079).

Conclusion: Pediatric pain service teams provide excellent inpatient pain management following primary palatoplasty. Proper transition from inpatient to outpatient can be achieved through parent education of pain management strategies and filling narcotic pain prescriptions prior to discharge. This transition protocol improves parent and patient satisfaction.
ABSTRACT
Re-evaluation of Team Based Learning sessions in Systems-Based Curriculum

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Supported by: McGovern Medical School Curriculum committee
Key Words: team based learning, medical school curriculum, systems based curriculum

BACKGROUND
Team-based learning (TBL) was introduced to McGovern Medical School as an instructional method in the new systems-based curriculum in 2016. There were 19 TBL cases in total, presented on a weekly basis over the span of the first semester. The TBL cases were designed to introduce problem solving sessions in a collaborative group environment, building upon the topics discussed through lecture content presented each week.

SIGNIFICANCE
An evaluation was administered to the pilot first year class after they had completed all TBLs to gain a clearer idea of their TBL experience. The strengths and weaknesses of the TBL system were gathered from this data and used in this project to improve the subsequent TBL sessions.

METHODS
An outline of the ideal TBL case was designed, and a rating system was created to highlight what factors of TBL were most important to the learning process. The following factors were evaluated for each case and given a rating based on the quality: the case introduction lecture (2 pts), the pre-reading assignment (1pt), and the TBL case exercises (2pts). Each TBL was given a rating out of 5, which helped gauge the level of improvement necessary for each case. This also helped highlight which cases were the most ideal and could later serve as a model for the ones rated more poorly. Cases were also evaluated based on how well they integrated with that week’s lecture topics and how appropriate they seemed for the level of first year medical students, with reference to the learning objectives covered by the guidelines for the USMLE Step 1 exam.

RESULTS
Each case was reviewed carefully and a list of changes to be made were discussed with the appropriate faculty responsible for each case. The changes were implemented and the current class of first year students are attending the new sessions. Data from the new class will be gathered in October 2017.

CONCLUSIONS
Although data has not yet been collected from the current class, it is believed that improvement of TBL sessions will greatly increase student understanding of the topics covered and provide an overall benefit to student learning.
ABSTRACT

Blood Product Utilization after Acute Non-Compressible Hemorrhage below the Diaphragm: Evaluation of the Impact of Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) on Emergent Blood Product Use

MEGAN MONT  McGovern Medical School at UTHealth  Class of 2020

Sponsored by:  Laura J. Moore, M.D., John Harvin, M.D., Charles E. Wade, PhD
Supported by:  McGovern Medical School Department of Surgery; CeTIR
Key Words:  REBOA, non-compressible hemorrhage, blood product

Background: Noncompressible hemorrhage is a leading cause of death in trauma patients. Aortic occlusion (AO) is a potentially life-saving adjunct in the resuscitation of hemorrhagic shock patients and can be performed via resuscitative thoracotomy, exploratory laparotomy, or Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) [1-3]. In patients suffering from hemorrhagic shock, temporary AO via REBOA may offer the advantage of decreasing the amount of blood product required while awaiting definitive hemorrhage control by supporting cardiac/cerebral perfusion and diminishing aortic inflow to the area of injury. We hypothesized that patients that undergo REBOA with balloon inflation at Zone 1 (thoracic aorta) will require fewer blood products during the first 24 hours as compared to case matched controls that do not undergo REBOA.

Methods: We conducted a propensity score matching analysis of trauma patients undergoing emergent laparotomy from October 2011 to July 2017 at the Red Duke Trauma Institute. Patients who received REBOA were matched to those who did not based upon their propensity scores, which were determined based upon the following variables: year of operation, attending surgeon, age, gender, mechanism of injury, arrival physiology, arrival coagulation profile, focused abdominal sonography for trauma results, and injury severity via injury severity score (ISS) and abbreviated injury scores (AIS). Our primary outcome was units of red blood cells (RBC) transfused during laparotomy.

Results: During the study period, 1,263 patients underwent emergent laparotomy and 61 (5%) of these patients also underwent preoperative Zone 1 REBOA. Based upon propensity scores, 37 REBOA patients were matched to 37 non-REBOA patients. The matching appeared adequate as the propensity scores, demographics, injury severity, and arrival physiology were similar between the two groups. A comparison of the results is presented in Table 1. The median intra-operative RBC transfused was significantly higher in the REBOA group (median 12 units IQR [6, 22] vs 6 units IQR [1, 12], p=0.006). Upon closer inspection, the REBOA group did not appear to be a similar group to the non-REBOA group. The REBOA group had a higher rate of estimated blood loss (median 2,250 cc IQR [550, 4,750 versus 900 cc IQR [250, 2,250]), p=0.097), damage control laparotomy (51% vs 38%), deaths due to hemorrhage (46% vs 21%), and intra-operative deaths (29% vs 8%). The REBOA group also had a lower rate of definitive laparotomy (19% vs 54%) and a higher number of deaths due to traumatic brain injury (36% vs 19%).

Conclusion: In this study, we aim to use the largest observational dataset available in the United States to determine the treatment effect of REBOA on intra-operative RBC transfusions. While the two groups appear similar in terms of propensity scores, demographics, injury severity, and arrival physiology, there appear to be confounding factors that are not accounted for in the analysis, such as patient selection for REBOA and the trauma surgeon’s clinical identification of patients’ severity of injury. The only manner to account for these potential confounding factors is randomization and a prospective, randomized controlled trial is necessary to obtain an accurate treatment effect of REBOA.
<table>
<thead>
<tr>
<th>Variable</th>
<th>No REBOA (n = 37)</th>
<th>REBOA (n = 37)</th>
<th>p value</th>
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<tbody>
<tr>
<td>Head AIS</td>
<td>2 (0.4)</td>
<td>3 (0.4)</td>
<td>0.754</td>
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<td>ED SBP</td>
<td>91 (72,110)</td>
<td>82 (67,107)</td>
<td>0.224</td>
</tr>
<tr>
<td>ED Base Excess</td>
<td>-10 (-18, -4)</td>
<td>-11 (-16, -8)</td>
<td>0.381</td>
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<tr>
<td>ED % Lysis</td>
<td>1.8 (0.1, 7.6)</td>
<td>4 (0.7, 60)</td>
<td>0.151</td>
</tr>
<tr>
<td>First OR SBP</td>
<td>107 (80,128)</td>
<td>85 (72,105)</td>
<td>0.026</td>
</tr>
<tr>
<td>First OR pH</td>
<td>7.23 (7.07, 7.34)</td>
<td>7.14 (7.05, 7.23)</td>
<td>0.028</td>
</tr>
<tr>
<td>First OR Lactic Acid</td>
<td>4.0 (2.5, 8.1)</td>
<td>7.5 (4.9, 10.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>First OR Base Excess</td>
<td>-6 (-14, -1)</td>
<td>-10 (-15, -6)</td>
<td>0.056</td>
</tr>
<tr>
<td>OR RBC transfusion</td>
<td>6 (1, 12)</td>
<td>12 (6, 22)</td>
<td>0.006</td>
</tr>
<tr>
<td>OR FFP transfusion</td>
<td>6 (0, 12)</td>
<td>10 (5, 22)</td>
<td>0.052</td>
</tr>
<tr>
<td>OR platelet transfusion</td>
<td>6 (0, 12)</td>
<td>12 (6, 18)</td>
<td>0.042</td>
</tr>
<tr>
<td>OR EBL</td>
<td>900 (250, 2250)</td>
<td>2250 (550, 4750)</td>
<td>0.0097</td>
</tr>
<tr>
<td>Mortality</td>
<td>14 (37%)</td>
<td>27 (73%)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

**Table 1.1**

**References**

ABSTRACT

Does Surveillance Bias Impact the Incidence of Deep Venous Thrombosis and Pulmonary Embolism at US Trauma Centers?

VICTORIA MORRIS  McGovern Medical School at UTHealth  Class of 2020

Sponsored by: Bryan A. Cotton, M.D., M.P.H., F.A.C.S., Department of Surgery
Supported by: CeTIR and McGovern Medical School Dean’s Office
Key Words: DVT, PE, Trauma, Screening

Background and Significance:
Venous Thromboembolism (VTE) is one of the most common complications of trauma patients and is a significant cause of mortality and morbidity\(^1\). VTE includes both deep vein thrombosis (DVT) and pulmonary embolism (PE) and can affect up to 600,000 patients a year\(^2\). In addition to third-party payers, many public and private agencies consider VTE incidence to be a marker for quality of care\(^3\). However, multiple studies have shown that rates may be affected by variability in screening practices, and that increased screening yields higher incidence\(^4,5,6\). We set out to evaluate the incidence of both DVT and PE at Memorial Hermann Hospital, considering current screening practices for VTE post-trauma.

Specific Aim: Evaluate Memorial Hermann Hospital’s DVT/PE rate and rate of screening tests order per patient.

Design and Methods: Retrospective cohort study, examining VTE events, screening Duplex ultrasound, and screening CT-angiograms (CTA) of the chest per patient. Highest level-trauma activations over the age of 15 years admitted between 1/1/2016 – 12/31/2016. Excluded those who died in the first 24 hours, those who were pregnant, and those with >20% TBSA burns.

Results: 1314 patients met inclusion; 37 (2.8%) with PE and 27 (2.1%) with DVT. 201 patients had a CTA and there was a total of 451 CTAs performed; 8.2% of CTAs were positive. The median number of CTAs in patients with PE was 2 (1, 3) versus 0 (0, 0) in those without PE; \(p<0.001\). 95% of PE patients had at least one CTA versus 13% of those without PE, 80% of PE patients had at least two CTAs versus 11% of those without PE, and 30% of PE patients had at least three CTAs versus 3% of those without PE; all \(p<0.001\). Of the 201 PE’s, 13% were main pulmonary, 36% were lobar, 24% were segmental, and 27% were subsegmental. 141 patients had a Duplex scan and there was a total of 190 Duplex scans performed. 14.2% of Duplex scans were positive. The median number of Duplexes in patients with DVT was 1 (1, 2) versus 0 (0, 0) in those without DVT; \(p=0.003\). 85% of DVT patients had at least one Duplex versus 9% of those without DVT and 30% of DVT patients had at least two Duplexes versus 2% of those without DVT; both \(p<0.001\). Controlling for age, male gender, and injury severity, the number of CTAs was independently associated with an OR of 2.6 for finding a PE, while the number of Duplex ultrasounds was associated with an OR of 4.6 for finding a DVT.

Conclusions: The rate of VTE events in trauma centers is dependent on the intensity of screening for these events. An adjustment should be made for intensity of screening for these significant events when assigning scores for hospital performance and for reimbursement, least government,
insurance, and quality organization discourage physicians and their hospitals from searching for these morbid and sometimes fatal events.

**Future Work:** Validation of event rates at other US trauma centers.
Dermatological Disorders in ESRD Patients: Effect on Quality of Life

CRYSTAL NWANNUNU       McGovern Medical School at UTHealth       Class of 2020

Sponsored by:  Donald A. Molony, MD Department of Internal Medicine
Stephen K. Tyring, MD, PhD, MBA Department of Dermatology
Supported by:  National Institute of Diabetes and Digestive and Kidney Diseases,
2T35DK007676-24
Key Words:  End stage renal disease, Dermatologic disorders, Quality of life

Background: Patients on hemodialysis due to end stage renal disease (ESRD) have an increased risk and often present with disorders of the skin, nails and hair. Published research notes common cutaneous presentations in ESRD, but the presentation frequency in hemodialysis patients and its impact on patient quality of life (QOL) is less well understood.

Hypotheses: Dermatologic disorders in hemodialysis patients negatively impact patient QOL. Treatment for these dermatologic disorders can improve patient QOL and overall care.

Methods: A 20 question multiple choice survey was developed in consultation with a nephrologist. The survey consisted of a patient perspective outcome measure to elicit the types of prevalent disorders of the skin, nails and hair, impact on QOL and satisfaction of physician care toward the patient’s dermatologic conditions. The survey was verbally administered to 39 adult ESRD patients undergoing chronic in-center hemodialysis at Davita PDI North and Davita PDI South in Houston, Texas. The results were recorded in Qualtrics survey software. A regression analysis was performed to assess association between dermatologic manifestations and QOL impact.

Results: Of the total participants, 33 (85%) presented with dermatological manifestations, with 31 (94%) experiencing skin disorders, 10 (30%) experiencing nail disorders, and 12 (36%) experiencing hair disorders. When asked if their cutaneous disorders negatively impacted QOL and if receiving treatment for their disorders could yield improvement, 24 (73%) and 18 (55%), respectively, gave affirmative responses. 24 (73%) participants were satisfied with their physician’s execution of care and concern for their dermatologic disorders. Regression analysis showed association between dermatologic disorders and negative impact on QOL in these hemodialysis patients.

Conclusion: Dermatological disorders experienced by ESRD dialysis patients negatively impact their QOL. One-fourth of ESRD dialysis patients were dissatisfied with their nephrologist’s care for their dermatologic disorders. When focused solely on one specific specialization, physicians can neglect the additional adverse effects patients experience increasing cognitive bias. Addressing the dialysis patient’s dermatologic concerns in addition to
their routine dialysis treatment can steer current/future physician treatment practice towards a better holistic execution, improving patient QOL and satisfaction with their physician care.
ABSTRACT

Comparable Responses in Male and Female to Cerulein-Induced Pancreatic Injury and Recovery

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Sponsored by: Tien C. Ko, MD, Yanna Cao, MD, Department of Surgery.
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5T35DK007676-24
Key Words: Chronic Pancreatitis, Cerulein, Male, Female

Introduction: A higher incidence of chronic pancreatitis (CP) in males has been reported in human studies. Whether CP is reversible and whether sex factor influences CP recovery, remains unclear. Cerulein, a cholecystokinin analogue that induces CP, is a commonly used and replicable CP mouse model. Using the cerulein CP model for a simulated period of CP injury and recovery, we tested our hypothesis that sex-dependent differences would occur during CP injury and recovery. Methods: Adult C57BL/6 mice were administered cerulein (n=3-6/sex/group, 50µg/kg, 5x hourly/day, 3 days/week, ip) for 4 weeks, then allowed a 4-week recovery period. Normal saline was injected as control. Body weight was recorded weekly. Pancreata were harvested, either 4 days (injury group) or 4 weeks (recovery group) after the last injection and weighed. Pancreatic paraffin sections were stained for hematoxylin and eosin, and parenchymal acinar injury was scored. Fibrosis was assessed by Sirius Red staining for extracellular collagen deposition. Macrophage infiltration was evaluated by CD68 immunohistochemistry. Results: From week 3-4 and 2-6, male and female mice injected with cerulein weighed less than their time matched controls, respectively (p<0.05). Four days after CP induction in injury groups, compared to the control groups, pancreatic injury was shown (respective to males, females) by decreased pancreas weight/body weight ratio (-50, -55 %), increased acinar injury score (+3, +3), increased fibrosis (15, 11 % additional area/field), and increased macrophage infiltration (8, 23 additional cells/field). Both males and females displayed similar responses on acinar injury and fibrosis, while females exhibited a 3-fold greater macrophage infiltration than males (p<0.05). Four weeks after CP induction in recovery groups, pancreatic recovery occurred (respective to males, females) with a recovery of pancreas weight/body weight ratio (29, 33 %) and reversal of acinar injury (95, 100 %) and fibrosis (61, 45 %). Similar recovery responses for these parameters were observed in both males and females. A full reversal of macrophage infiltration was observed in females and males. Notably, the time-matched control for the recovery mice, possessed higher baselines of macrophage infiltration than CP injury group. Conclusion: Male and female mice gained less body weight with induction of cerulein, but both showed recovery to normal weight after withdrawal of insult. Cerulein-induced acinar injury is reversible, while fibrosis is partially reversible. Both male and female mice demonstrate comparable responses in CP injury and recovery, except for macrophage infiltration. Time-matched groups should be used in animal design models for CP, to account for potential aging factors, as the control group, possessed higher baseline infiltration than the CP injury group.
ABSTRACT

The Clinical Spectrum of Patients with a Novel Heterozygous p.G366A Mutation in POLG1

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Class of 2020

Sponsored by:  Mary Kay Koenig, M.D. & Rahmat Adejumo, MBBS., MPH  
Department of Pediatrics

Supported by:  Mary Kay Koenig, M.D. & Rahmat Adejumo, MBBS., MPH  
Department of Pediatrics

Key Words:  mitochondrial disorder, POLG1, pol-γ, depletion syndrome

Background:  The electron transport chain is the essential cellular process for performing oxidative phosphorylation of ADP to ATP (Lamperti & Zeviani, 2016). Mitochondrial disorders are a group of clinical diseases that result from defects in the mitochondrial electron transport chain. The inheritance pattern of mitochondrial disorders can be autosomal dominant, autosomal recessive, x-linked, or maternal with mutations occurring either in the nuclear or mitochondrial DNA (Hudson & Chinnery, 2006). POLG1 is a nuclear gene encoding the catalytic subunit of the mitochondrial polymerase gamma (pol-γ). POLG1 is the only enzyme known to replicate mitochondrial DNA in humans and is one of the most commonly mutated genes affecting mitochondrial function (Di Fonzo et al., 2003). POLG1 mutations prevent proper proofreading during mitochondrial DNA replication and, over time, patients develop a depletion of their mitochondrial DNA producing increasing numbers of non-functional mitochondria. Disease is inherited via either autosomal dominant or autosomal recessive changes. The clinical spectrum varies greatly both between and within families (Tang et al., 2011). Herein, we describe the clinical presentation of a family carrying a novel heterozygous POLG1 mutation (c.1097G>C; p.G366A).

Methods:  We performed a phenotype-genotype study, using patients from the University of Texas Mitochondrial Center of Excellence. Patients with the c.1097G>C (p.G366A) mutation in POLG1 were included (HSC-MS-09-0057).

Results:  A total of four patients within the same family were identified with the c.1097G>C (p.G366A) mutation in POLG1. A muscle biopsy from the mother illustrated decreased levels of mitochondrial DNA (29% of control), confirming the diagnosis of a depletion syndrome. The mother had mild cognitive impairment. Other symptoms onset in her mid-30s, including diabetes mellitus, chronic constipation, gastric neuropathy, gastro-esophageal reflux disease, hypertension, and migraine headaches. Her two sons are also cognitively impaired and have symptoms of congenital heart defects, dysphagia, seizures, myoclonus, and tremors. Her daughter developed symptoms at age 7 years, initially presenting with muscle spasms and weakness in her lower extremities. In her early-20’s she is now pre-diabetic.

Conclusion:  The genotype-phenotype correlation of POLG1 mutations is poorly understood. Dominant mutations appear to produce a milder phenotype however symptoms vary greatly in severity and age of onset. We presented here a family of four carrying a novel POLG1 mutation [c.1097G>C (p.G366A)] producing a mitochondrial depletion syndrome. The most
common clinical symptoms noted in our patient pool were cognitive impairment, seizures, gastrointestinal dysfunction, diabetes mellitus, and myopathy.
ABSTRACT

Localizing Refractory Pediatric Epilepsy using Resting State MRI

LUDOVIC PAO

McGovern Medical School at UTHealth

Class of 2020

Sponsored by: Manish N. Shah, MD, Pediatric Neurosurgery
Supported by: Manish N. Shah
Key Words: Epilepsy, Localization, Resting State MRI

Epileptic seizure foci have been shown to affect resting state brain networks. This novel retrospective study aims to correlate resting state functional MRI (rsMRI) signal latency with pediatric epileptogenic foci lateralization.

rsMRI and anatomical MRI scans were obtained from 80 prospectively registered epilepsy patients and 585 control patients from the ADHD 200 data set. The MRI scans were preprocessed and registered using standard rsMRI techniques. Latency maps were generated by voxel-wise maximal cross-covariance parabolic interpolation of rsMRI signal lag and the global signal. Statistical maps were created for each epilepsy patient using control mean and standard deviation maps. By applying z-value thresholds to statistical maps, two-tailed hypothesis testing was performed. Threshold values were obtained via uncorrected thresholds ($\alpha=0.05, 0.01, 0.005, 0.001$), false discovery rate (FDR, Benjamini-Hochberg, $q=0.05$) and family-wise error rate (FWER, Bonferroni, $\alpha=0.05$) methods, the former two correcting for multiple comparisons. Significantly latent areas were counted for right and left hemispheres. The hemisphere with more latent areas was predicted to contain the seizure foci. To determine prediction accuracy, postoperative imaging was examined for procedure type and lateral side. A greater than 50% prediction rate in all but one test was observed (FDR for Lesion/Lobectomy=50%). A 100% prediction rate was observed for the most specific test per procedure. Some latent areas were local to seizure foci when qualitatively examined alongside postop images.

rsMRI temporal latency analysis has shown promise in lateralizing and localizing seizure foci. Additional prospective, multicenter studies will further characterize the relationship between signal latency and epileptogenic foci.
ABSTRACT

Abnormal Routine Preoperative Laboratory Tests in Outpatients’ Endoscopies at MD Anderson Cancer Center

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McGovern Medical School at UTHealth

Sponsored by: Linh T. Nguyen, MD, Department of Anesthesiology and Perioperative Medicine

Supported by: Linh T. Nguyen, MD

Key Words: Endoscopy, anesthesia, gastroenterology

BACKGROUND: Laboratory tests are conducted perioperatively often as a means of assessing the safety of a procedure for a patient and predicting possible adverse outcomes. Lab tests are classified as routine if they have no specific purpose, or indicated if for a specific clinical purpose. At MD Anderson Cancer Center, the patient population generally has a more significant medical history. Outpatients undergoing endoscopies under anesthesia may be more likely to have abnormal lab results that may lead to adverse outcomes compared to outpatients at other general practices. Therefore, the Anesthesia Assessment Center at MD Anderson orders routine lab tests including electrolytes, BUN, creatinine, complete blood count, and thyroid panels for all outpatients scheduled for an endoscopy under general anesthesia. This study aims to examine the frequency of abnormal routine lab tests and evaluate their predictive value for adverse perioperative events in outpatient endoscopies under general anesthesia at a tertiary cancer center. We hypothesize that the routine preoperative labs are not necessary for a safe anesthetic in patients undergoing outpatient endoscopies under general anesthesia, and eliminating them can result in cost savings.

METHODS: This retrospective study includes all adult (18 years and above) outpatients with endoscopic procedures under general anesthesia at MD Anderson Cancer Center from June 16th, 2015 until January 15th, 2017. The procedures included in this study are esophagogastroduodenoscopy (EGD), colonoscopy, percutaneous endoscopic gastrostomy (PEG), endoscopic ultrasound (EUS), and endoscopic retrograde cholangiopancreatography (ERCP). Lab results within 1 month prior to the patients’ procedure will be retrieved from ClinicStation and Epic EMRs. The following data was gathered if present within 2 weeks after the procedure: cancelled procedures, post-procedural complications, cardiology, neurology, or pulmonology consultations, hospital admissions, emergency center visits, chest X-Rays, cardiac markers, and MRI or CT of the brain. Additionally, deaths within 1 month following the procedure were also gathered.

ANALYSIS: Descriptive statistics will be used to analyze the patients’ demographic data alongside the lab values and post-operative outcomes. Students t-Test will be used for continuous variables, and the chi-squared test for comparing the categorical values. The sensitivity, specificity, and positive predictive value (PPV) will be estimated for each abnormal lab value in determining adverse perioperative events.
ABSTRACT
Assessing the Use of Fecal Microbiota Therapy in the Treatment of Multidrug-Resistant Enterobacteriaceae

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Sponsored by: Dr. Herbert Dupont, MD, & Dr. Zhi-Dong Jiang, Ph.D, University of Texas School of Public Health
Supported by: NIH-NIDDK grant
Key Words: Multidrug resistance, extended-spectrum beta-lactamase, fecal microbiota therapy

Fecal Microbiota Transplant (FMT) is a novel approach to eliminating antibiotic-resistant Enterobacteriaceae in patients harboring multi-drug-resistant microbiota. It is hypothesized that FMT therapy markedly reduces abundance of multi-drug resistant bacteria such as extended-spectrum-beta-lactamase E.coli (ESBL) and/or vancomycin-resistant Enterococcus (VRE) in the gut microbiological compositions of patients with recurrent infection of Clostridium difficile (rCDI) with significant dysbiosis. A retrospective study on 136 subjects diagnosed with rCDI and treated with FMT was conducted to evaluate the efficacy of FMT in the eradication of invasive microbiota. 22 samples were positive for extended-spectrum beta lactamase resistance at the initiation of FMT and 14 recovered from ESBL by the date of last collection (3 from 30 days for FMT-1 and 11 from 90 days after FMT-2) (3 lost to follow-up). Out of 71 samples that were positive for VRE at the time of initiation of FMT, 37 of the patients resolved by the last sample collected (9 at 30 days for FMT-1 and 28 at 30 days for FMT-2) and 8 were lost to follow-up. The efficacy of FMT on a portion of the patients warrants further study into the use of this therapy to successfully treat individuals with recurrent multi-drug-resistant infection.
ABSTRACT

DIEP flap breast reconstruction performed at a small, community based safety-net hospital, with comparison of outcomes to the American Society of Plastic Surgeons Tracking Operations and Outcomes for Plastic Surgeons programs.

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Sponsored by: Daniel J. Freet, M.D., Department of Plastic & Reconstructive Surgery
Supported by: Department of Surgery, Dean’s Office stipend
Key Words: Breast reconstruction, DIEP flap

Deep Inferior Epigastric Perforator (DIEP) flap breast reconstruction is an improved method of autologous tissue breast reconstruction with reduced insult to the abdominal wall, but at the same time requiring increased technical skill. This study summarizes the peri- and post-operative data collected on 64 patients that have undergone DIEP flap breast reconstruction. In our patient population, 6.25% experienced total flap loss, 3.13% experienced partial flap loss, and 0% experienced complications such as pulmonary emboli, septic shock, urinary tract infection, surgical site infection, myocardial infarction, cardiac arrest, stroke, coma, and death. This compares to a total flap loss rate of 2.71% and a partial flap loss rate of 1.51% in the American Society of Plastic Surgeons Tracking Operations and Outcomes for Plastic Surgeons (ASPS TOPS) data base over the last 5 years. Rates for our other peri-operative complications were all below or equal to those recorded in the TOPS database. Higher rates of total and partial flap loss at LBJ we suspect is due to resident physicians who have not mastered the fine art of microsurgery performing the vascular anastomoses. In addition, recognition of vascular compromise could be slower than necessary to revascularize and save the flap. We believe that with more education and training, DIEP flap surgeries could be safely offered to a wider patient population at LBJ Hospital in the near future.
ABSTRACT

An Investigation into the Mechanical Properties of Articular Cartilage

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Sponsored by:  Catherine G Ambrose, Ph.D., Department of Orthopaedic Surgery
Supported by:  NIH/NIDDK Grant, #2T35 DK007676-24
Key Words:  Mechanical Properties, biomechanics, articular cartilage, tissue engineering

Current orthopedic clinical practice for osteoarthritis attempts to relieve pain, aid repair, or delay damage using non-steroidal anti-inflammatory drugs, steroid injections, or hyaluronic acid injections. Following these palliative actions the clinician’s main recourse is synthetic total joint replacement. However, we are entering a new era where a biological, tissue engineered replacement is becoming feasible. There are several different methods used by researchers to test articular cartilage, but these methods vary widely and have not been standardized to ensure comparable results. In this study, we sought to standardize these by providing an outline for efficient articular cartilage testing that is easily repeatable. Crucially, these experiments lay the groundwork to establish standard testing methods for tissue-engineered cartilage prior to implantation. Testing these mechanical properties in first bovine, and then across human tissue samples, allows us to create a standard with which to compare future tissue engineered constructs. The data obtained from the bovine mechanical testing can be used to compare to both other types of cartilage as a standard of the values that healthy cartilage should have, as there is a high degree of similarity between bovine and human articular cartilage mechanical properties. We tested these samples under various conditions, such as exposure to collagenases for different amounts of time to change their collagen content, levels of which can be assessed biochemically and histologically. We tested their compression and viscoelastic properties, as these have the most relevance to in vivo stress using compressive stress relaxation. These tests were run on an Instron 5848 using a 100N load cell and an unheated water bath with Phosphate Buffered Saline for the stress relaxation test. The cartilage was isolated with a diamond-coated drill bit with a 7/16” diameter and equilibrated with a vibratome to ensure even thickness. We applied compressive strains of 5, 10, 15, and 20% for 20 minutes each to assess the stress strain curves. This gave us a range of values for various content percentages of the collagen matrix proteins and the respective change on the mechanical properties of the underlying cartilage. Our data showed clearly that exposure to collagenase, even for short periods of time, caused significant structural changes and differences in the mechanical properties. The slope of the asymptotes of the stress-strain curve produced under these settings was different than that of untreated cartilage, and the difference was correlated with time of exposure. These results indicate a standard of testing that may be easily repeated in future testing of human articular cartilage as well as tissue engineered constructs.
Abstract
Pregnancy shows beneficial effects on dystrophic mice

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Sponsored by: Aiping Lu, MD, Department of Orthopedic Surgery
Supported by: Aiping Lu, MD
Key Words: DMD, dKO-heterozygous, MDX, pregnant, multi P

Introduction: Duchenne Muscular Dystrophy (DMD) is a genetic disorder characterized by the complete loss of dystrophin [1]. It currently has no cure despite the continued understanding of the disorder. It was previously shown by our lab that pregnancy improves the myogenic differentiation of myogenic progenitor cells (MPCs) in vitro and improves muscle regeneration in wild type (WT) mice in vivo. In this study, the effects of pregnancy were observed in MDX mice, which is a mouse model for DMD. To rule out hormonal effects present during pregnancy, dKO-heterozygous (dystrophin-/-/utrophin+/-) mice, which is another mouse model for DMD, that were previously pregnant up to five times (multi P) in the past were compared to virgin mice. Muscle histopathology was performed to compare the mice. Our results suggest that pregnant MDX mice and that previously pregnant dKO-heterozygous mice had overall better outcomes when compared to their controls. The results show that pregnancy has beneficial effects for dystrophic mice and that changes in the dystrophic microenvironment could be an approach to improve muscle weakness, despite the lack of dystrophin expression.

Methods: Animals: MDX pregnant mice that were pregnant (gestational age between 10-18 days) and non-pregnant mice of the same age were sacrificed. Multi P and virgin dKO-heterozygous mice of the same age were sacrificed. The gastrocnemius muscle was isolated, frozen, and sectioned.

Histochemistry: H&E and trichrome staining were performed. Trichrome was done to observe collagen deposition levels to assess the amount of fibrosis present.

Immunohistocytochemistry: Sections of muscle were fixed with 5% formalin. Mouse IgG, embryonic myosin heavy chain (e-MyHC), and F4/80 were used as markers with the Vector® M.O.M.™ immunodetection kit. Mouse IgG was used to observe muscle fiber necrosis. Newly regenerated myofibers were observed with e-MyHC. F4/80 was used to evaluate macrophage infiltration.

Results: Decreased fibrosis in pregnant MDX mice: Through trichrome staining, less fibrosis was seen in pregnant MDX mice when compared to the virgin control, which indicates circulating factors present during pregnancy are responsible for the marked improvement (Fig. 1A, 1B). Increased muscle regeneration and decreased inflammation in pregnant MDX mice: Through immunostaining with e-MyHC and F4/80, increased muscle regeneration and decreased macrophage infiltration were observed in pregnant MDX mice, respectively (Fig. 2). However, by staining with mouse IgG, we observed that the amount of necrotic fibers was not lower in pregnant MDX mice (data not shown). Increasing the number of mice is needed to confirm this.
Better outcomes in multi P pregnant dKO-heterozygous mice: The results showed that multi P dKO-heterozygous mice muscle had less fibrosis and a lower number of necrotic fibers compared to the virgin control (Fig. 3) These results help disprove hormonal effects being a factor.

Discussion: Current treatment methods for DMD do not lead to full recovery; therefore, new alternatives are continually being investigated. Little has be done to look into changing the muscle microenvironment in DMD patients as a therapeutic approach. Parabiosis has be useful in revealing the ability of circulating factors in young mice to assist in muscle regeneration potential in older mice [2]. Pregnancy is a form of natural parabiosis and has shown to have a positive effect in WT mice with cardiotoxin injury [2]. The results of this study have shown that pregnancy also provides beneficial effects in the muscle of dystrophic mice. Additionally, during this study, dystrophic mice that were not pregnant, but had undergone multiple pregnancies in the past, were compared to virgin controls. The previously pregnant dystrophic mice had increased muscle regeneration. The results support the idea that hormonal effects were not the only reason for the better outcomes observed with pregnancy, but that presence of other circulating factors were upregulated due to pregnancy. DMD only affects males, but this study helps to prove a concept and develop a treatment for DMD patients. Future studies with increased sample sizes should be done to definitively determine if pregnancy assists in reducing the effects of muscular dystrophy disorders.

Significance: This study can lead to the development of novel and clinically relevant therapies for DMD patients.

References:
**Abstract**

**Introduction**
There is already ample evidence showing that an Enhanced Recovery After Surgery program is effective in expediting patient recovery in various surgical specialties. Enhanced Recovery after Spinal Surgery (ERSS) for major spine surgery program was instituted at a tertiary cancer center. This program includes, but is not limited to, multimodal care involving nurses, dieticians, and physiotherapists alongside anesthesiologists and surgeons, adequate peri-op pain relief, early post-op ambulation, reduction in surgical stress, optimal intra-operative fluid therapy, and a change in anesthetic technique. Our hypothesis is that an ERSS approach would decrease ICU stay and thus ultimately reduce the cost burden.

**Methods**
A total of 220 major spinal surgical cases observed, 65 were non-ERSS cases (managed without the ERSS protocol) and 163 were ERSS cases (managed with ERSS protocol).

**Results**
The number of ICU admissions for open spine surgery were 16 out 163 in the ERSS group (9.8%) and 14 out 65 in the non ERSS group (21.5%) resulting in an 11.7% absolute reduction in post-surgical ICU admissions for open spine surgery.

**Conclusion**
At this tertiary cancer hospital, implementation of ERSS program has helped decreased the utilization of post-operative ICU care resulting in cost savings. A methodological review of ICU costs in the United States in 2010 estimated the cost per day in the ICU was $4,300, contrasting with a Healthcare Cost and Utilization Project (H-CUP) analysis stating that the average non-ICU cost per day for a cancer patient in 2009 was $3,300. With the implementation of the ERSS program, an estimated $1,000 per day of non-ICU admission per patient was saved.

**References**
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ABSTRACT

Will flipping the classroom improve student satisfaction and student performance in the pre-clerkship curriculum?

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Sponsored by: Allison Ownby, Ph.D., ME.d., Educational Programs

Supported by: McGovern Medical School Summer Research Program in the Office of Educational Programs

Key Words: Medical Education, Flipped Classroom, Active Learning

Introduction: The “Flipped Classroom” (FC) is a model of instruction that allows students to engage in higher order thinking and more active learning in the lecture hall. In this model, a teacher assigns pre-class work and then engages in interactive activities in class that animates the pre-class assignments. This model is centered on the idea that class time is more effective when students are actively engaging with the material as opposed to passively receiving information from a teacher. There is evidence that active learning is more beneficial for student comprehension in science courses. To better understand whether the flipped classroom could benefit McGovern Medical students (MMS), Dr. Carpenter and I worked this summer to “flip” five of the standard biochemistry lectures from Block 1 of Foundations.

Methods: Data were collected by surveys via Qualtrics and Block 1 summative performance via ExamSoft. All data were collected anonymously and are reported in aggregate. There was a pre and post-test survey and a survey after the four flipped classroom sessions. The first-year medical students were asked to complete an anonymous two-question pre-test survey before their first flipped classroom session. This survey asked about the student’s perceptions of the flipped class model. Students then had to complete a 5-question survey at the end of each flipped class which asked about the effectiveness of the video and use of class time. Students were then asked to complete another two-question survey after the block 1 summative exam asking about their perception of the FC model again.

Results: The pre-test vs post-test survey indicates that students preferred the flipped classroom model as opposed to the traditional lecture. In the first survey, 6 students (19.35%) preferred a flipped classroom while 13 students (41.94%) preferred a traditional lecture. In the post-test survey 40 students (57.14%) preferred the flipped classroom as opposed to 16 students (22.86%) who preferred the traditional lecture. These two surveys indicate that students grew to prefer the FC model of learning as opposed to the traditional lecture. After the first flipped class, 111 students (46.64%) strongly agreed that class time was used effectively while 95 students (39.92%) somewhat agreed. In the second flipped class 118 students (69.82%) strongly agreed.

that the class time was used effectively while 36 students (21.30%) somewhat agreed. The last two after class surveys are still being interpreted. From the first two after class surveys, most students believed that the FC model was an effective use of their time. Summative examination data are still being analyzed, but from the preliminary paired t-test conducted, results suggest that while there was improvement in performance scores, differences were not significant.

Conclusion: From this study, students in the pre-clerkship curriculum at MMS believe the FC model of learning is effective and most students have grown to prefer this model. Research should be focused on expanding this model of learning to other classes in the pre-clerkship curriculum.
ABSTRACT
Impact of Smoking on Trauma Patients Expected to Receive Massive Blood Transfusion

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Sponsored by:  Charles E. Wade, PhD
Supported by:  Center for Translational Injury Research
Key Words:  Trauma, Smoking

Background: Thirteen percent of all Americans smoke and/or use tobacco products. This percentage is higher in the trauma population. The adverse long-term effects of smoking are well documented. The cardiovascular literature describes the phenomena of the “Smoker’s Paradox” where smokers who undergo acute myocardial infarctions (MI) have overall lower short-term mortality, though no difference or worse outcomes long term. The current literature is divided on the impact of smoking and tobacco use on the trauma population. We hypothesized that patients with severe traumatic injuries who smoke will have worse outcomes in terms of mortality, length of stay, and complications.

Methods: We conducted a retrospective analysis of patients who were enrolled in the PROPPR study. The PROPPR study was a multi-institutional study that looked at the effects on mortality and morbidity of two transfusion protocols in patients expected to receive massive blood transfusions. Patients were divided into two groups based on known tobacco use. Multivariate analysis for mortality was assessed for 24 hours and 30 days taking into account ISS score, blunt vs. penetrating, head AIS score, PROPPR treatment group, age, etc. In addition, cytokine data were analyzed.

Results: There were no differences in basic demographics (p> 0.05) between smokers (n=140) and non-smokers (n=540): median (IQR), Age= 35 (26, 49.5) vs 33.5 (24, 51), ISS= 24 (14, 34) vs 29 (18, 41), RTS= 6.90 (5.03, 7.84) vs 6.61 (4.09, 7.84). After accounting for site, age, mechanism of injury, ISS score, AIS head, and PROPPR treatment, smoking was associated with overall lower mortality at 24 hours (OR=0.09, p<0.001) and at 30 days, with the primary difference occurring at < 6 hours (OR=0.04, p=0.002) in contrast to ≥ 6 hours (OR=0.48, p=0.037). Deaths due to exsanguination/hemorrhage or TBI were decreased in smokers (1.4% vs 15.6%, p<0.001 and 3.6% vs 10.6%, p<0.01, respectively). Admission cytokine levels of IL-6 (p=0.002) and MCP-1 (p=0.012) were significantly lower in the smoking group. Serum cotinine, a metabolite of nicotine, levels for the mortality group will be measured to confirm smoking status.

Conclusions: Smoking appears to have a protective effect in the severely injured trauma population, reducing early deaths as a result of hemorrhage or TBI in patients living to hospital arrival. This may be due to an attenuation of the early inflammatory response.
ABSTRACT

Surgical Drains and Their Influence on Patient Recovery Following Equatable Plastic Surgeries

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Sponsored by: David J. Wainwright, MD; UT Physicians Plastic and Reconstructive Surgery
Supported by: UT Physicians Department of Plastic and Reconstructive Surgery
Key Words: Surgical drains, tubing length, patient outcomes

BACKGROUND: The use of post-operative surgical drains is indicated in patients who have an accumulation of fluid or prophylactically in patients who are at a high risk for developing fluid-related complications following a surgical procedure. Drawbacks to their use include an increased risk of post-procedure infections and increased duration of hospital stays. Furthermore, early removal of surgical drains equates to better outcomes and reduced rates of infection. Complications of surgical drains include occlusion of tube, site infection, clot formation, and poor placement resulting in hernia or perforation. A review of the literature found that most existing studies evaluating surgical drain management have addressed the necessity of drain use overall, and not alterations in the drain or its care to generate improved outcomes. This prospective research study was designed to assess how a drain factor (e.g., tubing length) can affect patient outcomes post-operatively.

MATERIALS AND METHODS: Patients who were undergoing any plastic surgery operations that stipulated the use of bilateral drains were recruited into this study. A total of 14 patients over the span of three months were enrolled in this study. Upon initiation of incision closure following the completed surgery, the fenestrated end of the Jackson-Pratt drains were placed bilaterally and symmetrically in the generated open space. Side randomization was established through a blind choice by an objective observer, and one tubing was cut to a 60 cm length and the other tubing was cut to 30 cm. Before leaving the operating suite both drains were emptied and their initial volume measured. For their post-operative course, patients were given a demonstration on proper drain emptying and care, and given both a drain emptying schedule and evaluation forms covering associated factors such as pain, inflammation, infection, and convenience. Once drain volumes decreased to less than 50 cc per 24 hours the drains were removed in-clinic and an exit interview covering full drain experience was conducted.

RESULTS: Four out of fourteen patients in the current sample size experienced greater drainage volume from the 60 cm drain vs the 30 cm drain with the mean percent increase being 16.5% (2.6-39.9%). Ten out of fourteen patients had greater drainage volume from the 30 cm drain vs the 60 cm with a mean percent increase of 28.3% (16.1-36.8%). While the mean average drainage volume for the 30 cm group was larger than that of the 60 cm group, this was found to not be statistically significant (p=0.24). In addition, two patients experienced greater pain in the 30 cm drain site in comparison to the opposing 60 cm site, and four patients experienced greater clotting in the 60 cm drain site versus the 30 cm side.
CONCLUSION: While more patients enrolled in this study experienced greater drain output on average from a Jackson-Pratt drain cut to 30 cm versus their 60 cm counterparts, this margin was found to not be statistically significant. Therefore, we would fail to reject the null hypothesis which is that no clinical difference exists between patient outcomes when utilizing a 30 cm drain tubing in comparison to a 60 cm drain tubing. Also, there appears to be a tendency for shorter drains to have increased pain, and this is speculated to be due to being pulled on more often. Longer drains were shown to have a trend of clotting, which is likely due to the nature of increased length allowing for more area to clot. The relatively low power (0.45) of this study may have contributed to the failure to reject the null hypothesis. Further data collection and increased sample size may serve to illustrate an appreciable difference.
ABSTRACT

Pulmonary Surfactant Protein-A Induced Degradation of Toll-Like Receptor-4 Through the Ubiquitin-Proteasome Pathway

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Sponsored by:  
Joseph L. Alcorn, PhD, Department of Pediatrics

Supported by:  
National Institute of Diabetes and Digestive and Kidney Diseases,  
5T35DK007676-24

Key Words:  
Necrotizing Enterocolitis, Surfactant protein A, UPP

Background:  
Necrotizing enterocolitis (NEC) is a disease that affects 7% of premature newborns (weighing between 500 – 1,500 g) with a 20-30% mortality rate. NEC is characterized by severe inflammation of the gastrointestinal lining which has been shown to be largely mediated by toll-like-receptor-4 (TLR4). Surfactant protein A (SP-A) is mainly produced in the lungs where it plays an immunomodulatory role on TLR4 activity and expression. In a previous study using a mouse model of NEC, gavaged SP-A reduced both TLR4 and IL-1β in the ileum. The exact mechanism of this downregulation is not elucidated; however, it has been observed that the proteasome inhibitor MG132 ablated the ability of SP-A to decrease TLR4 expression. So I hypothesized that exposure of gastrointestinal epithelial cells to SP-A leads to degradation of TLR4 through the ubiquitin proteasome pathway (UPP).

Methods:  
SP-A was extracted and purified from previously collected bronchioalveolar lavage during the first few weeks. Gastrointestinal epithelial cell lines HT-29 (Human colonic cell line) and IEC-6 (Rat intestinal cell line) were incubated in the presence or absence of SP-A and in the presence or absence of various proteasome inhibitors (MG-132, bortezomib, or carfilzomib). The expression of TLR4 was detected using western immunoblot analysis. Immunoblots were treated with TLR4 and β-actin antibodies. Bands were visualized with chemiluminescence and quantified using a storm 840 phosphor imager.

Results:  
Adding the proteasome inhibitor bortezomib did not increase TLR4 levels in either HT-29 or IEC-6 cell lines as expected, and instead decreased TLR4 even further compared to cell lines incubated with SP-A alone. Similarly, TLR4 expression failed to increase in cell lines treated with carfilzomib and MG-132.

Conclusion:  
The use of proteasome inhibitors was expected to cause an increase in TLR4 expression relative to cells treated solely with SP-A; however, MG-132, bortezomib, and carfilzomib all failed to ablate the ability of SP-A to downregulate TLR4. This leads us to believe that TLR4 is not being degraded through the ubiquitin proteasome pathway as previously thought, but instead depends on lysosomal proteolysis. For this reason, future studies should concentrate on lysosomal inhibitors chloroquine, bafilomycin, and the endocytosis inhibitor dynasore to test this newfound hypothesis in our system.
ABSTRACT

Cytochrome B reductase 1 (CYBRD1) in red blood cells (RBC) of patients with hemoglobin SC (HbSC) and hemoglobin SS (HbSS) forms of sickle cell disease (SCD).

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Sponsored by: Richard J. Kulmacz, PhD, Department of Internal Medicine
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5T35DK007676-24; American Heart Association, 16GRNT29170013

Key Words: cytochrome B reductase 1, sickle cell disease, hemoglobin SC

BACKGROUND: HbSC (HbS (α2βS2) and HbC (α2βC2) compound heterozygote) individuals account for 15% of SCD patients in the US. HbSC individuals generally have milder clinical manifestations than HbSS patients, but the reasons for this difference are not completely understood. SCD pathology results from chronic cycles of ischemia / reperfusion, exacerbated by the consequently increased vascular oxidative stress. Ascorbic acid, an essential plasma antioxidant, tends to be depleted in SCD patients. CYBRD1, a RBC membrane protein, regenerates plasma ascorbic acid through an electron transfer mechanism. Recent reports have shown that HbSC RBCs experience oxidative stress that is intermediate between HbSS and HbAA RBCs. Initial immunoblot results from our lab suggested that HbSS RBCs have less CYBRD1 than HbAA RBCs (healthy controls), and CYBRD1 isoform patterns on immunoblots suggested there was less post-translational modification in CYBRD1 from HbSS RBCs. Thus, we hypothesized that RBC CYBRD1 levels and isoform patterns in HbSC patients would be intermediate between those of HbSS patients and HbAA controls.

METHODS: Blood samples were collected at UTHSCH Comprehensive Sickle Cell Center from HbSC (N=6) and HbSS (N=8) patients, and healthy African American volunteers (N = 8). Procedures for isolation of RBC membranes and quantitative immunoblot analysis of CYBRD1 content and isoform distribution have been described. (Kulmacz et al. (2015) Blood 126, 2170)

RESULTS: HbSS (N=5) and HbSC (N=4) RBCs had similar CYBRD1 levels (1.13 ± 0.20 vs 1.06 ± 0.24 ng/µg membrane protein, respectively; P<0.7). No difference was seen in CYBRD1 content between HbSS and HbAA (N=5) (1.13 ± 0.20 vs 1.18 ± 0.20 ng/µg membrane protein, respectively; P<0.7) or between HbAA and HbSC samples (1.18 ± 0.20 vs 1.06 ± 0.24 ng/µg membrane protein, respectively; P<0.4). However, the CYBRD1 modification index values were significantly different: HbAA, 80 ± 7 % N=8; HbSS, 61 ± 8 % N=8 (P<0.0002 vs. HbAA); and HbSC, 73 ± 4 %, N=6 (P<0.006 vs. HbSS; P<0.06 vs. HbAA).

CONCLUSIONS: Our findings do not support the hypothesis that RBC CYBRD1 content differs between HbAA, HbSC, and HbSS RBCs. However, we believe that known differences in hematocrit between HbAA, HbSC, and HbSS individuals will still lead to differences in the total amount of circulating CYBRD1, and thus the total ascorbate recycling capacity. Our
observation of differing CYBRD1 isoform patterns between healthy controls and SCD patients raises the possibility of altered regulation of CYBRD1 function in SCD patients.
ABSTRACT
Interprofessional Education through Standardized Patient Cases

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Sponsored by: Jennifer L. Swails, M.D., Department of Internal Medicine
Supported by: In part, U.T. System Patient Safety Committee Medical Education Grant
Key Words: Interprofessional Standardized Patient Simulations

According to the Joint Commission, poor communication contributed to 62% of sentinel events reported in 2012-2014. In response to this opportunity to improve patient safety, the major accrediting bodies for medical professionals require that students be prepared “to function collaboratively on health care teams.” Our project aimed to utilize interprofessional (IP) standardized patient (SP) cases to improve students’ communication and teamwork skills. A team of IP faculty from each of the five UT Health professional schools was recruited to collaborate in designing two SP cases. A simulated electronic medical record was created for each case in Practice Fusion. Students completed assignments in Canvas, including pre- and post- tests, online teamwork skills lectures, a review of relevant medical literature, and a worksheet each team filled out during the case. The students were tasked with completing the Interprofessional Collaborative Competency Attainment Survey (ICCAS) before and after the cases. Team work skills were evaluated by the SPs using checklists and through verbal SP feedback to each team. Students offered feedback about the case both verbally and electronically through the Canvas website.

A pilot group of 38 students participated in the SP simulations in April 2017. An additional 92 students participated in one of the two cases in July 2017. The pretest ICCAS was completed by 99% of the assigned students and 78% of the students completed the post-test ICCAS. The average ICCAS scores were compared using a two-tailed nonpaired t-test and both cases showed significant improvement. For the in-patient case, the pretest average was 5.32 and the post-test average was 6.57 with a p-value of <0.05. For the ambulatory case, the pretest was 6.17 and the post-test was 6.73 with a p-value of <0.05. Subjective student feedback emphasized the importance of the patient and the team in providing optimal care.

These cases were implemented into the curriculum of the medical school, dental school, and nursing school, with continued participation of students from public health and bioinformatics schools on a volunteer basis.
Progressive hemorrhagic injury and traumatic brain injury inflammation in the context of polytrauma

BRADLEY ROWLAND McGovern Medical School at UTH ealth Class of 2020

Sponsored by: Charles E. Wade PhD, Center for Translational Injury Research (CeTIR)
Supported by: CeTIR
Key Words: Traumatic brain injury (TBI), Progressive hemorrhagic injury (PHI), inflammation

Progressive hemorrhagic injury (PHI), the early expansion of intracranial hemorrhage presumably secondary to derangements in coagulation and inflammation, is a devastating complication of traumatic brain injury (TBI). Studies exploring PHI pathophysiology in polytrauma, which itself is associated with secondary inflammatory aberrations, are limited. We predict that PHI is associated with greater clinical inflammation compared to patients with polytrauma or stable hemorrhage (SH) alone.

We retrospectively reviewed a cohort of highest-level activation trauma patients with prospectively collected data. Using radiological and clinical criteria, patients were separated into SH with polytrauma (n=7), PHI with polytrauma (n=23), or polytrauma alone (n=54). Data for standard demographic and clinical variables were collected via chart review. Inflammatory cytokine/chemokine marker profiling was conducted across 8 timepoints in the first 72 hours of admission. Data was compared for TBI vs. non-TBI patients and PHI vs. SH patients using Cox 24hr mortality model, univariate analysis, and Fisher’s exact test.

Patients with TBI demonstrate significantly greater inflammation for IL-6, IL-8, MCP-1, and G-CSF from 2-12hrs after admission compared to non-TBI. PHI was associated with higher mortality (p = 0.0309) and demonstrated significantly greater inflammation in IL-6, IL-8, MCP-1 and G-CSF (p < 0.05). Increasing levels of IL-6 was associated with a two-fold increased risk of mortality (HR 2.06, 95%CI 1.35-3.14, p = <0.001).

Patients with PHI demonstrate exaggerated inflammatory responses and have poorer clinical outcomes including mortality. These novel findings provide a molecular understanding of PHI specific inflammatory dysregulations; thus, yielding targets for improved intervention and biomarkers for improved prognostication.
ABSTRACT

Determinations of Coagulation Kinetics Using a Novel Linear Thromboelastometry Device

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Key Words:  
TEG, Thromboelastography, Thromboelastometry, Trauma, Novel Device

Introduction:  
Thromboelastography (TEG) demonstrates clinical utility in multiple surgical fields including general, trauma, hepatic, and cardiac surgery. We describe a novel linear thromboelastometry device (LTD) driven by a microelectromechanical system (MEMS) with the potential for scaling to portability. The LTD demonstrates similar coefficients of variation as TEG in normal human control subjects. We hypothesize that this device will correlate with TEG values in trauma patients.

Methods:  
Venous blood was collected from healthy adult volunteers and Level 1 trauma patients into citrate tubes. Recalcified blood is injected into a well mounted on a MEMS driven translational stage. As the blood clots, and a platelet/fibrin mesh forms, an increasing force acts on the unfixed end of a paddle probe inserted in the sample. This force is measured optically as deflection of the probe. Clot formation metrics were defined as follows: maximum amplitude of probe deflection (MA), time to first evidence of probe deflection (R), and time to reach an established deflection (K). Blood from a single individual was tested in triplicate for 3 consecutive days to determine single person variability of the device. To test population variability of the device, blood from four individuals was tested in duplicate. To test the sensitivity of the device, blood samples were diluted with phosphate buffered saline (PBS). 11 Level 1 trauma patients were tested in the LTD and TEG to demonstrate their correlation.

Results:  
Coefficient of variation (CV) is smaller in the LTD than TEG for R (CV=0.232, CV=0.294) and K (CV=0.230, CV=0.435) in single person variability and MA (CV=0.045, CV=0.095) in population variability. Hemodilution with PBS demonstrated a strong correlation between platelet count and MA in the new device ($R^2 = 0.978$), and LTD MA correlated strongly with TEG MA ($R^2 = 0.934$). The new device detected a signal in as little as 5% blood by volume, while TEG detected a signal at 15% blood by volume. There was a strong correlation between TEG MA and LTD MA in the trauma patient population (Pearson r=0.6854, P<0.05).

Conclusion:  
This preliminary study demonstrates repeatability and clinical relevance of the LTD. The LTD shows a strong correlation with TEG values in trauma.
ABSTRACT
Lymphatic Contribution to Peripheral Arterial Disease and Chronic Venous Disease

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Sponsored by: Eva Sevick-Muraca Ph.D., John Rasmussen Ph.D., Center for Molecular Imaging

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 2T35DK007676-22

Keywords: Lymphatics, Peripheral Artery Disease, Chronic Venous Disease, Peripheral Vascular Disease

Peripheral Arterial Disease (PAD) and Chronic Venous Disease (CVD), are leading causes of disability in people older than 50 years of age. Evidence suggests that the lymphatics contribute to the etiology of PAD and CVD. In PAD, functioning peri-adventitial lymphatics are essential for reverse cholesterol transport in arterial walls, preventing plaque accumulation. Likewise in CVD, reduced numbers of lymphatic vessels and increased lipids have been found in the adventitia of incompetent veins with varicosities. If lymphatic dysfunctions are found to contribute to PAD and CVD, then therapeutic strategies to modulate the immune-lymphatic system could be used to help manage PAD and CVD. This project evaluates lymphatic anatomy and function of 40 patients with early CVD (CEAP 0-4) and/or mild to moderate PAD (Rutherford 2-5 disease) using near-infrared fluorescence lymphatic imaging (NIRFLI). To do so, indocyanine green (ICG) was administered intradermally in the lower extremities after which, NIRFLI is performed by illuminating the skin with diffuse laser diode light and collecting filtered fluorescent light emanating from the ICG-laden lymph. Using NIRFLI images, lymphatic anatomy and function were analyzed in early CVD and PAD patients. In each of three subjects imaged to date, evidence of lymphatic dysfunctions including dermal backflow, and dilated, tortuous, and/or segmented lymphatic vessels, and impaired lymphatic pumping was found. The PAD subject with Rutherford stage 3 disease presented with non-linear vessels, dermal backflow, and lymphatic reflux in both legs. The first of two CVD subjects presented with C3 disease on the right leg and C5 disease on the left leg. The right (C3) leg presented with segmented and dilated vessels. In the left groin there was dermal backflow, suggesting lymphatic congestion. However the etiology of congestion is unknown and it cannot be concluded that this congestion contributes to or is a result of the CVD. Lymphatic pumping was present bilaterally, but was infrequent. The second CVD subject presented with bilateral C4 disease. The lymphatics in the left and right legs were segmented and dilated, though vessels were better defined in the left leg as the right leg exhibited possible dermal backflow. Pumping events were frequent, but with 50% more pumping events in the left leg. The segmented vessels in the subjects may be a result of lymphatic varicosity or unequal accumulation of ICG within individual lymphangions. The reflux found in the PAD subject suggests lymphatic valve dysfunction. Reflux was observed in a prior patient with an arterial component to their disease. Whether lymphatic reflux is a hallmark of PAD may be better determined as more PAD subjects are enrolled. Using NIRFLI, lymphatic dysfunction has been
observed, as compared to previously imaged healthy subjects. As this study continues, evidence is growing that lymphatic dysfunction is involved in the etiology and/or progression of PVD and CVD.
ABSTRACT

Biomechanical Study Analyzing the Maintenance of Interfragmentary Compression with a Position Screw

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Sponsored by: James F. Kellam, MD; Catherine Ambrose, PhD; Department of Orthopedics, McGovern Medical School

Supported by: James F. Kellam, MD; Catherine Ambrose, PhD; Department of Orthopedics, McGovern Medical School; McGovern Medical School- Office of The Dean

Key Words: Position, screw, maintenance, interfragmentary, compression

Introduction: Interfragmentary fracture site compression enhances fracture union by increasing the fracture site contact area, enhancing fracture stability and decreasing the stress on the orthopedic implant. Lag screw fixation is the gold standard in achieving interfragmentary compression. However, in certain circumstances it may be an ill-advised technique such as in osteoporotic bone, possibly leading to iatrogenic fracture and fixation failure. In these cases, a position screw is recommended. A position screw holds the fracture fragments in the reduced position only. Utilizing this technique can make operating in certain circumstances where lag screw placement is difficult much easier, saving time, money and potential complications.

Objectives: The aims the study are to prove that: 1) the compressive force generated by a reduction clamp can be maintained by the position screw and 2) a conventional lag screw will maintain the reduction clamp generated compression force and not dissipate on clamp removal.

Methods: Twelve 4th generation composite bone models had identical 45-degree oblique fractures created. Commercially available self-tapping bone screws (thread diameter of 4.5mm and a core diameter of 3.2 mm) were used. One group of 6 models was designated as the “lag screw” group (LS) and one was designated as the “position screw” group (PS). For the LS, a glide hole of equal diameter to the screw thread diameter was drilled perpendicular to the fracture site in the near cortex and then the thread hole (diameter equal to screw core diameter) was drilled in the far cortex. For the maintenance screw group, the same technique is employed but no near cortex glide hole is drilled, thus creating no compression. For each bone, the simulated fracture was reduced and stabilized with a reduction clamp tightened to the maximal compression force manually. Two Tekscan pressure sensors (in N) at 180 degrees to each other were placed between the two fracture fragments to measure the compression as the clamp and respective screws were applied and the results were averaged. The clamp was then removed and another measurement was recorded.

Results: For the PS group, clamp compression yielded an average force of 169.9 N across six trials (N=12 to account for two sensors per trial). Screw and clamp compression yielded an average force of 122.3 N. Screw only compression yielded an average force of 42.4 N. An ANOVA and Tukey post-hoc test found that the mean forces of screw group was significantly different from the other two groups but there was no significant difference between the clamp/screw and clamp. For the LS group, (N=11 because one sensor did not read measurements so its values were eliminated) clamp
compression yielded an average of 93.4 N. Clamp and screw compression yielded an average of 272.1 N. Screw only compression yielded an average force of 259.6 N. The ANOVA and Tukey post-hoc test found that the mean forces of the screw only and clamp/screw group were not significantly different from each other. However, there was a significant difference between the clamp only group and the others. A graphical depiction of these results can be found in Figure 1.

**Conclusion:** While the lag screw will maintain and greatly increase the compression force generated by the reduction forceps, a position screw cannot maintain the compressive force generated by the clamp. In fact, as demonstrated by our data, the compressive forces with the position screw significantly decreased when it was inserted with the clamp in place and decreased even more when only the screw was present. We surmise that this is because the threads of the position screw are on both sides of the fracture site, distracting the fracture site and reducing interfragmentary compression. In summary, the position screw is not an adequate replacement for the lag screw to hold the compressive force generated by a reduction clamp. Further studies should be conducted in cadaveric bone to see if this conclusion holds true.

**Appendix:**

Figure 1. Mean compressive forces generated for each type of compression across six trials using a maintenance screw.
Figure 2. Mean compressive forces generated for each type of compression across six trials using a lag screw.

Note: SE= Standard Error.
★ denotes significant difference between two groups (p <.05).
ABSTRACT

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Sponsored by:  Leorah Freeman, MD, PhD, Department of Neurology  
Supported by:  FCMSC Grant/Scholarship Award + UTHealth Department of Neurology  
Key Words:  Enhanced Regional Cerebral Perfusion Following Acetazolamide: Preliminary Results

Enhanced Regional Cerebral Perfusion Following Acetazolamide: Preliminary Results

Background: Clinical symptoms in multiple sclerosis (MS) typically occur as a result of focal inflammation associated with demyelination and axonal damage within white matter lesions. Symptoms can be transient for many patients during the initial stage of the disease with some varying degrees of clinical improvement, dependent upon whether inflammation subsides and tissue undergoes repair. Observational studies have shown that these alterations in tissue perfusion were evident prior to regional atrophy, suggesting that a primary abnormality in the cerebral vasculature might contribute to cerebral hypoperfusion, and evolution of MS pathology. If reduced cerebral perfusion is important in disease progression, then improving blood flow might lessen, or even reverse this process, thus favoring repair. While transient increases in CBF are noteworthy and documented, sustained change in CBF might be necessary to impact lesion evolution and potentially limit or partially reverse clinical disability.

Hypothesis: Acetazolamide (ACZ) has a good safety and tolerability profile, and is known to enhance cerebral perfusion. Our central hypothesis is that ACZ may provide long-lasting global increases in CBF and thus have sustained beneficial effect on focal lesion outcome.

Significance: There are currently several potent disease modifying therapies (DMTs) available to treat patients with MS which have all been shown to decrease the potential for new injury. Despite their anti-inflammatory properties, DMTs are not known to alter cerebral perfusion and no therapy has thus far been rigorously evaluated to show whether improved blood flow affects lesion evolution in MS patients.

Methods: The perfuseMS study (NCT02466074) is a placebo-controlled trial to evaluate the effect of long-term ACZ therapy on lesion evolution in MS patients. Stage 1 is designed to determine the magnitude of change in cerebral perfusion after a single intravenous (IV) infusion of ACZ. Eligible patients have stable MS either treatment naïve or on platform therapies. Absolute cerebral blood flow (CBF) was measured using pseudo-continuous arterial spin labeling (pCASL). Five MS patients received pCASL at baseline and 15, 30, 60, 90, 120, 150 and 180 min after a single IV bolus of 1 gm ACZ. pCASL was performed with a single shot gradient echo EPI sequence (TR/TE of 4300 ms/16 ms, voxel size 3 × 3 × 5 mm, number of dynamics 70, label duration 1900 ms, post label delay 2000 ms). Data were analyzed
with FMRIB Software Library and FreeSurfer v5.3.0. After partial volume correction, CBF maps were registered to 3D-MPRAGE images using boundary-based registration. Brain regions were segmented using semi-automated methods into cortex, normal-appearing white matter (NAWM), deep gray matter (DGM) and T2-hyperintense lesions.

**Results:** Consistent with prior reports in healthy subjects, our patients had 30%-62% increase in global CBF 15 min after ACZ. Unlike prior reports, global increases in CBF were present for up to 180 min. Increases in CBF were seen in all brain regions. CBF in cortex increased 26%-54%, NAWM by 25%-53% and DGM by 31%-74% at 15 min. While greater variability was seen in absolute CBF within lesions, the largest increases were found with 14%-105% occurred at 15 min. Similar to global kinetics, increases in CBF within brain regions were present for up to 180 min.

**Conclusions:** We report for the first time the kinetics of cerebral perfusion in MS patients following 1 gm IV ACZ challenge. Though greatest change in cerebral perfusion might be expected in the cortex, we found substantial increases in CBF in various brain regions including cortex, NAWM and DGM. We also found robust increases in CBF within MS lesions; areas considered injured. These results show that blood flow can be increased to lesioned tissue and supports further investigation of our hypothesis that cerebral hypoperfusion is important to lesion evolution and improving cerebral perfusion might impact tissue repair.
ABSTRACT

Put a Ring on it: Better Pediatric Pre-Induction Checklist Adherence Observed with Parent Engagement

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Sponsored by:  Dr. Kuojen Tsao, MD, Pediatric Surgery
Supported by:  Dr. Kuojen Tsao, MD
Key Words:  Checklist adherence, parent engagement

Introduction:  Patient and parent engagement in healthcare has been shown to improve compliance and outcomes in many medical disciplines, but no literature exists regarding parent engagement in the perioperative process. The World Health Organization surgical safety checklist (SSC) recommends including the parents of pediatric patients in checklist completion. At our children’s hospital, the pre-induction SSC is conducted in pre-operative holding with anesthesia, nursing and often with parents. We hypothesized that better checklist compliance would be observed when parents were engaged in checklist performance.

Methods:  An observational study of pre-induction checklist adherence during non-emergent pediatric operations was performed from 2016 to 2017 during two separate 8-week periods. Adherence was defined as verbalization of each checkpoint with or without parent confirmation. Six of 13 checkpoints (patient identification, procedure, surgical site marked, weight, allergies and NPO status) containing information relevant to parental knowledge were evaluated for staff confirmation with parents. Trained observers assessed parent engagement based on: parents off their phones, not distracted, positive body language, eye contact and demonstrating an understanding of the checkpoint. Chi-square test and linear regression were used for analysis. P-value <0.05 was significant.

Results:  Over the study period, 459 pre-induction checklists were observed with at least partial completion in 93.3% of cases with kappa >0.7. The mean proportion of checkpoints completed was 64.6% ± 31.1% and the proportion of fully completed pre-operative checklists was only 18.3%. Parents were present in 82% of cases and at least 1 checkpoint was confirmed with parents in 79% of checklists. Pre-induction checklist adherence was better when parents were present compared to when absent (p<0.001 for all checkpoints). Linear regression demonstrated a 1.2 (95%CI 1.0-1.3) increase in pre-induction adherence for every unit increase in parent engagement (Figure). Furthermore, meaningful completion of checkpoints by staff confirmation with parents differed significantly based on parent engagement with 93.9-100% of staff confirmation of checkpoints occurring with engaged parents compared to 0.3-6.1% in parents deemed not engaged (p<0.001).

Conclusion:  Pre-induction SSC performance remains a challenge, as less than one-fifth of checklists were completed in full. However, dramatic improvement in compliance and staff confirmation of checkpoints was observed when parents were present for and engaged in the
checklist process. Creating a process and training operative teams how to engage parents may increase checklist compliance and improve patient safety.
ABSTRACT

Use of autologous blood clot for human muscle derived stem cells preservation and growth

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Sponsored by: Xueqin Gao MD, PhD, Johnny Huard PhD, Department of Orthopaedic Surgery
Supported by: Start-up funding from Dr. Johnny Huard lab.
Key Words: Human muscle derived stem cells, blood clot, proliferation, apoptosis

Introduction: Previous study has shown the efficacy of fibrin clot in preserving the viability of human muscle derived stem cells (hMDSCs) when cultured in proliferation medium. The purpose of this study was to investigate if the fibrin clot itself can maintain hMDSCs survival without the use of proliferation media by culturing clot load with cells in PBS.

Methods: Six patients were recruited for the study and hMDSCs-Lenti-GFP(6X10^5) cells were mixed with 30ml whole blood drawn from clinical patients following the IRB protocol. The formed clot was squeezed to remove residual serum. Each clot was cut into 12 pieces and placed into two wells of 6-well plate. 5 mL of proliferation medium (PM) or PBS was added to the wells respectively. One piece of the clot was taken out at various time points (0h, 1d, 2d, 3d, 4d, and 7d) and embedded in NEG freezing medium followed by snap freezing via liquid nitrogen. Cryosections were cut. GFP immunofluorescent staining was used to detect hMDSCs in the blood clot. Cell proliferation in the blood clot was detected via Ki67/GFP double immunofluorescent staining. Fluorescent images were collected using Nikon-Ni upright microscope and quantified via Image J. Student t test was performed for comparison between the two groups. Average number of cells per time point in each group was normalized to a 200X magnification field.

Results: Our results showed that GFP positive hMDSCs can be found in the fibrin clot both cultured under PM or PBS for 7 days. Quantification of GFP hMDSCs positive cells demonstrated that there is no difference between clots cultured in PM and PBS at 0h and 1d. However, there are fewer GFP positive cells in PBS cultured clots at 2, 3, and 7 day time points compared to clot cultured in PM (P=0.0043, 0.0025, and 0.021 respectively for 2, 3, and 7 day time points). Ki67/GFP double positive cells showed no significant difference between PM and PBS group at any times points.

Discussion: Our results showed fibrin clot can preserve cell survival for a short time (1d) when they are cultured in PBS without any nutrients. The total number of cells decreased overtime when the clot was cultured in PBS as compared to that cultured in PM. Although blood clot cultured in PBS did not survive as long as that in PM, cell proliferation (Ki67/GFP double positive cells) has no difference. These results are meaningful, especially in a clinical setting. If the clot can keep cells alive in the first 24 hours, cells in the clot can get nutrients from the blood circulation and then be able to differentiate and repair tissues, such as meniscal tissue. Staining
for caspase 3 was also performed to determine if there is difference in cellular apoptosis between the PM and PBS group and is currently under analysis. We conclude that blood clots can be used as an autologous scaffold for hMDSCs mediated tissue repair.
ABSTRACT

Comparative Analysis of subdural grids vs. stereoelectroencephalography in the evaluation of intractable epilepsy

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Sponsored by: Nitin Tandon, MD, Department of Neurosurgery
Supported by: Nitin Tandon, MD, Department of Neurosurgery; McGovern Medical School – Office of Educational Programs

Key Words: Electrocorticography, Intractable Epilepsy, Epilepsy surgery, Complications, Efficacy

INTRODUCTION: Subdural Electrodes (SDE) have been the mainstay for the evaluation of patients with non-lesional or ill-defined focal epilepsy in North America. The advent of stereoelectroencephalography (SEEG) over the past decade has transformed the process of the localization of regions responsible for seizure onsets, for resection/ablation/neuromodulation, in a minimally invasive fashion. Both SDE and SEEG techniques have relative advantages, but in many patients, either one could be applied. We sought to compare the relative efficacy, morbidity and seizure outcomes following these two approaches.

METHODS: All 260 intracranial procedures, consecutively performed by a single neurosurgeon from 2004 to 2017, were identified using a prospectively compiled surgical database. Patient demographics, characteristics of epilepsy, duration of monitoring, procedural morbidity and eventual outcomes were determined. We computed the opiate requirements following each of these intracranial evaluations as a surrogate for the pain associated with each approach. Comparisons between groups were made using unpaired t-tests and chi-squared tests to evaluate distinctions.

RESULTS: Both SEEG (n=121) and SDE (n=139) groups were similar in age (30.1 ± 12.2 vs. 30.6 ± 13.8 years), gender (SEEG = 47.1% male; SDE = 43.9% male) and duration of epilepsy (16.4 ± 12.0 years vs. 17.2 ± 12.1 years). A much larger proportion of SDE patients (13.7%) received blood products during surgery compared with SEEG patients (0.8%) (p = 0.0001). Pain medication requirements were also much greater in the SDE vs the SEEG group (355.8 ± 232.9 mg vs 201.4 ± 175.5 mg). The duration of intracranial monitoring in these two groups was comparable (SEEG = 7.7 ± 3.9 days vs. SDE = 8.1 ± 2.8 days). Similar numbers of SDE (6) and SEEG (7) patients underwent placement of additional electrodes after the initial implant, during the same hospital stay, to further delineate the seizure onset site. There were 7 symptomatic hemorrhagic sequelae and two infections in the SDE cohort with no clinical complications in the SEEG cohort (p = 0.004). Only one patient from the SDE cohort experienced long-term neurological sequelae related to the intracranial evaluation. A greater proportion of SDE patients underwent resective or ablative surgery (91.4%), compared with SEEG patients (72.7%, p < 0.0001). None of the SDE patients and 4.1% of SEEG patients underwent placement of the RNS device. 8.6% of SDE patients and 14.1% of SEEG patients were not thought to be
candidates for further cranial intervention. The seizure outcomes (Engel I or II) in this group, at 6 months post-resection, trended in favor of SEEG (83.1%) relative to SDE (65.5%, p = 0.01).

**DISCUSSION:** SEEG and SDE have significantly distinct procedural morbidities: 6.5% (SDE) and 0% (SEEG), p < 0.05, associated with distinct pain medication requirements, which should factor into decision making when patients with pharmaco-resistant epilepsy are being considered for an intracranial evaluation. However, long term deficit rates related to either type of electrode placement are small. A smaller proportion of patients undergoing SEEG evaluations undergo resective or ablative surgery, likely related to the fact that some patients in this cohort may be distinct, less well localized epilepsy population compared to those undergoing SDE placement. There was a noticeable trend towards a better outcome in the SEEG cohort at 6 months post-resection (p = 0.01).
ABSTRACT

Role of Circulating Tumor Cells as a Biomarker of Disease Progression in Prostate Cancer Patients

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Supported by: Robert J. Amato, DO, Division of Oncology; The University of Texas at Houston Medical School—Office of The Dean
Key Words: Circulating Tumor Cells, Prostate, Cancer, Biomarkers

Introduction: Prostate Cancer is the most common cancer among men and the third leading cause of cancer death in men. While prostate specific antigen (PSA) remains an integral part of the clinical management of prostate cancer, there lies a need for a more sensitive and specific method of monitoring treatment response and cancer progression. Circulating tumor cells have gained significant interest in recent years and have potential to serve as a valuable biomarker for prostate cancer.

Methods: Blood samples were collected for 17 patients over multiple time points and processed using the AxonDx nCyte™ System. This system relies on a proprietary cancer cell detection cocktail in conjunction with an epi fluorescence scanning microscope for the enumeration of CTCs. Individual patient’s CTC counts were compared with longitudinal PSA measurements and radiographic findings.

Results: CTCs were enumerated from all 17 patients. CTC values were found to vary largely between patients and longitudinally in the same patient. CTC values ranged from 0-6.2 cells/ml. Of the 3 patients with greater than 4 CTCs/ml, 2 patients had evidence of active disease, either local viable tumor or bony metastases. One of these patients progressed and died of their disease. Of the 14 patients with CTC values that never went above 4 CTCs/ml, 2 patients had evidence of progressive metastatic disease and elevated PSA levels. For the remaining patients who did not have PSA or radiologic evidence of disease progression, CTC values obtained varied longitudinally, ranging from 0-3.5 CTCs/ml. In most cases, there appears to be little clinical significance in these fluctuations. For a few of these patients there was an isolated elevation in CTC value with a simultaneous falling PSA.

Discussion: This study demonstrates that there is a correlation between CTC values and the current disease state. Based on these findings CTCs show promise as an additional way of monitoring disease progression in prostate cancer patients. Future studies with a larger patient cohort should be conducted to establish the utility of CTCs as a biomarker of disease in prostate cancer patients.
ABSTRACT

Optimizing the Dosing of Chemotherapy Pharmacokinetics in Obese Cancer Patients

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Supported by:  HOPA Research Foundation  
Key Words:  Dosing, Chemotherapy, Obesity, Actual BSA, Assigned BSA, Capped BSA

Introduction: Obesity is associated with worse cancer outcomes. While determinants of response are multifactorial, poorer prognosis might be due to inadequate dosing through the common practice of using an assigned body surface area (BSA) to calculate chemotherapy doses in obese patients. In general, obesity is known to alter the volume of distribution and clearance of medications; however, there is limited pharmacokinetic data for most chemotherapy agents in the setting of obesity. Furthermore, many agents exhibit non-linear pharmacokinetic behavior, making it difficult to define and determine the impact of changes in dose on systemic exposure. The aim of this study is to understand the pharmacokinetic differences of the nonlinear agents, paclitaxel and cisplatin, in obese patients when dosed on actual versus assigned BSA or capped BSA. This data will be used to provide additional guidance for appropriate dose adjustments in clinical practice.

Methods: A total of sixty patients will be recruited to this study from the UTHealth-Memorial Hermann Cancer Center in the Texas Medical Center (TMC). Ten obese/overweight patients and ten control (non-obese) patients will be enrolled per study arm for each of the regimens being evaluated: paclitaxel + carboplatin once every three weeks (N=20), paclitaxel weekly + carboplatin (N=20), or cisplatin/XRT (N=20). For the first cycle, patients in the treatment group will be randomized into two groups with paclitaxel or cisplatin dose calculated based on either actual BSA or the respective assigned/capped BSA. They will receive the alternate BSA in the second cycle. For cycle 3 and beyond dosing is based on primary oncologist’s discretion. On the day of infusion for cycles 1 and 2, blood samples are collected for analysis via validated assays using either PaperSpray mass spectrometry or HPLC-UV for paclitaxel or atomic absorption for cisplatin. Toxicity is monitored using the MDASI QOL assessment tool for cycle 1 and 2 and chart notes are monitored through cycle 6.

Results: This study is still ongoing with anticipated enrollment to conclude in December 2018. To date 8 patients (3 obese, 5 control) have been enrolled on the paclitaxel + carboplatin once every three weeks study arm. More toxicity has been observed in this study arm. Three patients (1 obese, 2 control) have been enrolled on the paclitaxel weekly + carboplatin study arm. More toxicity has been observed in this study arm. Two patients (2 obese) have been enrolled on the cisplatin/radiation study arm. Collection of toxicity data for the cisplatin/radiation study arm
is ongoing. Analysis of differences in plasma concentrations for all patients is ongoing and will be presented on poster.

**Conclusion:** Preliminary results show that obese cancer patients who received full-weight based doses of paclitaxel and cisplatin have higher levels of toxicity compared to their normal weight counterparts. These results support using assigned BSA for the calculation of chemotherapy dosing in obese patients.
ABSTRACT

Prognostic Value of Ambulatory Blood Pressure Associated with Left Ventricular Hypertrophy in Children Evaluated for Primary Hypertension

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Key Words: ABPM, BMI, Pediatrics, Ambulatory

Hypertension is a prominent problem in both adult and pediatric populations. Ambulatory blood pressure monitoring (ABPM) is a 24-hour study that is the testing method of choice for analysis of pediatric blood pressure. The primary goal of this retrospective chart review is to identify correlations between ABPM summary statistics, including demographics, average BP, BMI and current medication regimen, and measures of heart function seen on echocardiography (Echo), specifically the presence of left ventricular hypertrophy (LVH). Chart review was done on all patients born after 1995 who underwent ABPM testing as patients of UTHHealth Pediatric Hypertension Clinic from January 1\textsuperscript{st}, 2015-December 31\textsuperscript{st}, 2016. Data analysis suggests that BMI is the only significant independent predictor of LVH, with other established factors like gender and clinical BP values showing insignificant correlation. This conclusion suggests that a change should be made in the primary criteria for cardiac work-up to place a stronger focus upon BMI.
ABSTRACT

Using Image Analysis Software to Assess Morphological Changes in Cutaneous Neurofibromas over the Course of Treatment with an mTOR Inhibitor

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Sponsored by: Keri Smith, PhD, Department of Pathology
Key Words: Neurofibromatosis, image analysis, pathology

Neurofibromatosis is a genetically inherited disorder resulting from defects in the Neurofibromin 1 (NF1) gene. Most adults with neurofibromatosis type 1 develop benign tumors that are composed of Schwann cells, fibroblasts, mast cells, and vascular components, and that manifest as cutaneous, spinal, or plexiform lesions.

Neurofibromin normally suppresses the oncoprotein Ras. When Ras protein remains unsuppressed, it activates the mTOR pathway which decreases apoptotic activity, causing cellular proliferation. Thus, we performed an interventional study to determine if treatment with oral mTOR inhibitor would reduce the size of cutaneous lesions in patients with neurofibromatosis. We hypothesized that mTOR inhibitor treatment would induce tissue remodeling in the cutaneous neurofibromas, causing changes in cell type and collagen composition in the lesions.

We obtained 4 mm punch biopsies of lesions were from subjects at initiation of treatment, 3 months, and 6 months, and the tissue was fixed in formalin, embedded in paraffin, and sectioned for H&E staining. Slides were digitized using a Motic Easy Scan Pro system, and 5 representative images at 20X magnification were saved for each biopsy. We identified 4 main cell types in the tissue sections based on shape and staining properties: round cells, comma cells, spindle cells, and mast cells. We selected 50-100 examples of each cell type to use as training sets for the learning algorithm built into inForm 2.1 image analysis software. All biopsy images were then analyzed to quantify cell types and collagen density.

The results of our image analysis revealed significant heterogeneity among lesions, with obvious changes over the course of treatment. Overall, there was a significant increase (p = 0.009) in collagen density after 6 months of treatment, and the density of collagen negatively correlated with the percentage of round cells in the tissue (p=0.007). Overall changes in cellular composition were not significant over time, with the exception of an increase in percentage of comma-shaped cells from 3-6 months of treatment. Although much is still unknown about the cellular components of neurofibromas, our results suggest that some level of tissue remodeling could be occurring within the lesions in response to treatment. Future studies should aim to determine specific activation pathways that are affected and how to efficiently target them.
ABSTRACT

Effects of Antihypertensive Medications on the Success of Kidney Transplantation

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Supported by: NIDDK/NIH T35; Cynthia Bell, Department of Pediatrics

Key Words: Antihypertensive, Kidney Transplantation, Allograft Failure

Introduction: Hypertension complicates the outcomes of kidney transplantation, leading to cardiovascular complications and decreased kidney graft survival. There are epidemiologic data to support a hypothesis that cardiovascular inflammatory state related to the type of antihypertensive therapy choice pre-transplant might impact allograft survival post-transplant. In this study, we explore the effects of antihypertensive use prior to kidney transplantation on graft survival and mortality. The major types of antihypertensives interrogated in this study are calcium channel blockers, thiazide diuretics, angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs), and beta blockers.

Hypothesis: We hypothesize that there will be significant differences in allograft outcomes of hypertensive patients based on their antihypertensive treatment prior to transplantation while on dialysis. There is evidence of improved vascular outcomes in hypertensive patients on ACEIs or ARBs which could translate into improved outcomes in transplant patients. Additionally, variation in antihypertensive use could potentially be an underlying contributor to discrepancies observed between genders, ethnicities, and/or diabetic status.

Method: We began the research on antihypertensive use on graft survival using the United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research Files from September 1987 to December 2013 with the permission from UNOS. Using STATA 14.1, we analyzed differences between kidney graft survival time between patients on antihypertensives and those who are not, excluding patients who were retransplanted, had simultaneous pancreas transplant, or who had no known antihypertensive status. Analyses were performed using the Kaplan-Meyer log rank test with three possible failure outcomes: (1) allograft failure (excluding graft survival after death), (2) allograft failure or death, or (3) death. We stratified the data for ethnicity, gender, and diabetic status. A p-value <0.05 was defined as statistically significant.

Results: One significant limitation we had during the first phase of our study was the limited antihypertensive medication data in the UNOS database. Thus, we require the USRDS database to access blood pressure management prescriptions. We are currently working on analysis for the USRDS dataset and do not have the final results available. With these results,
we hope to understand whether any differences exist between specific classes of antihypertensive treatment pre-transplantation and outcomes. These results might lead to improvements in the treatment of hypertension in the ESRD population. Clarification in which antihypertensive regimen provides superior outcomes will not only improve patients’ lives but also decrease the burden of allograft failure has on the health care system.
ABSTRACT

Hurry Up and Wait: Pre-Incision Delays in the Pediatric Operating Room Associated with Lower Adherence to Pre-incision Surgical Safety Checklist

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Key Words: Surgical safety checklist, quality of care, perioperative care

Introduction: Operating room (OR) delays impact patient flow and resource utilization. Surgical cases are commonly tracked for delays in the patient reaching the OR. Time spent in the OR before incision is not often evaluated. We hypothesized that low adherence to the pre-induction surgical safety checklist (SSC) may be associated with pre-OR delays or longer pre-incision times.

Methods: An observational study of a convenience sample of scheduled, elective pediatric surgical cases in a tertiary care children’s hospital was performed over two 12-week periods by trained observers. Specialties included general and thoracic, urology, neurosurgery, ophthalmology, orthopedics, otorhinolaryngology (ENT), and plastic and reconstructive surgery. Performance of the pre-induction checklist in the pre-operative area between nursing staff, anesthesia staff and patient/parents, the first phase of the SSC, was monitored. Degree of adherence to the pre-induction SSC is the proportion of checklist items completed. Pre-OR delays are institutionally defined as cases in which the patient enters the room more than 5 minutes after scheduled start. Pre-incision time was calculated as the difference between scheduled case start or room entry, whichever occurred first, and incision time. Descriptive statistics, chi², t-tests and linear regression were performed. Inter-rater reliability was determined before the start of study using Cohen’s kappa.

Results: Interrater reliability was greater than 0.70 for both years. Of the 451 observed cases, 34% had a pre-OR delay. Median total pre-incision time was 37 minutes (IQR 22-52). Mean pre-induction adherence was 84.6±21.7% and did not vary by specialty (p=0.12). Pre-induction adherence to the checklist (p=0.65) and specialty (p=0.11) were not associated with Pre-OR delays. First cases of the day were more likely to be on time (p<0.01). Longer total pre-incision times were associated with specialty (p=0.02) and worse checklist adherence (p<0.01, figure). After adjustment for specialty, case type and adherence, first cases (p<0.01), ENT specialty (p=0.03), and higher pre-induction adherence (p=0.03) remained associated with shorter pre-incision times.

Conclusions: While pre-OR delays are tracked and audited, delays in the OR before the start of surgery are not usually captured. Trying to achieve one metric of timeliness and efficiency may push the necessary preparations to the OR, ostensibly a more expensive locale. Pre-operative
readiness may be reflected by pre-induction checklist performance and better measured by total pre-operative time.
**ABSTRACT**

CT scan guided sizing in TAVI pre-procedural planning and post-procedural outcomes

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**Key Words:** Heart valve prosthesis implantation/instrumentation/methods; aortic valve insufficiency/diagnostic imaging; risk factors; transcatheter aortic valve replacement/methods; treatment outcome

**Objective:** The objective of this study is to identify anatomical factors, variations in implant technique that ensure successful implantation, and possible anatomical-procedural variations that have led to intraoperative complications.

**Methods:** We have retrospectively analyzed CT scan obtained from 261 consecutive patients who underwent TAVI with the S3-THV in our institution in 2016. TAVI patients were divided into groups based on annular anatomy and device size (20, 23, 26, 29 mm). CT annular area was calculated and utilized to determine size of the S3 valve to be implanted. Each implant was then subsequently matched with the degree of (if any) degree of aortic regurgitation (AI) after initial implant, the need of post dilatation due to residual AI after implant and the end of the procedure. Degree of post implant aortic regurgitation was determined by echocardiography at the time of procedure. Based on annular area specific volumes were determined to be loaded the initial delivery system.

**Results:** Out of 261 patients 37 were implanted with the 20-mm valve, 88 with the 23-mm valve, 101 with the 26-mm valve, and 35 with the 29-mm valve. Volumes at initial deployment were nominal (i.e. based on manufacture recommendation) in 96% of cases and preemptively adjusted in 4% of cases based on operator experience guided by CT & preoperative TEE. The 9 valves requiring preemptive adjustment in the deployment system ranged from -3 cc to +2 cc. Of this subset of patients (9/261), 66% (6/9) of valves showed mild insufficiency at initial deployment that was treated with post dilatation incremental volume (0.5 to 1.5 mL). For noted insufficiencies, the valve sizing distribution is as follows: one 20 mm, two 23 mm, two 26 mm, and one 29 mm valve. After post-dilatation, 100% of valves showed reduced AI with either trace or no leak.

Of the 247 valves deployed at nominal volumes, 85% (211/247) showed no signs of aortic insufficiency (central regurgitation nor paravalvular leak) at the time of deployment. The remaining 15% (36/247) showed the following insufficiencies: 31 mild, 4 mild-moderate, and 1 significant. 23% (8/35) of 20 mm, 15% (12/82) of 23 mm, 11% (11/97) of 26 mm, and 15% (5/33) of 29 mm valves showed insufficiency after deployment. 11% (29/247) of valves, all of which showed insufficiency, were post-dilated with variable incremental volumes in the deployment system; 14% (5/35) of 20 mm valves required post-dilatation; 12% (10/82) of 23 mm valves required post-dilatation; 10% (10/97) of 26 mm valves required post-dilatation;
12% (4/33) of 29 mm valves required post-dilatation with incremental volume (1 to 2 mL). After post-dilatation, 100% of valves showed reduced AI with either trace or no leak. 5 of the 261 TAVR procedures (1.9%) suffered significant complications, including 3 emergent ECMO placements and 3 pericardiocentesis procedures. These valves were deployed at nominal volume and were within indicated ranges for their respective annular areas (three 23 mm valves and two 26 mm valves). None were post-dilated.

**Conclusion**: Our current sizing strategy for S3 device on TAVI seems to be able to effectively eliminate significant the degree of post implant aortic regurgitation. Longer echocardiographic follow up will be needed to confirm our initial post procedural finding.
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